Hypnotic Drugs, Human Performance, and Ageing

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Contents

Page

Abstract

This thesis examines the effects of ageing on the use and on the behavioural impact of hypnotic drugs. Within this context, experiments reported here further examined the proposition that elimination half-life reliably predicts the occurrence and the magnitude of daytime behavioural impairment in older individuals following the repeated use of hypnotic drugs.

Evidence considered in Chapters 1 and 2 indicates that, while age is recognized as an influential subject variable in the drug-performance relationship, it has received little experimental attention.

Experiment 1 (Chapters 2, 3 and 4) evaluates the effects of repeated doses of two short acting hypnotics, triazolam 0.5mg and lormetazepam 1.0mg, and placebo both within, and between sub-groups of, middle-aged subjects.

Chapter 5 examines the clinical and experimental evidence which indicates that the elderly (65y+) are more susceptible to the behavioural side-effects of hypnotic drugs. The epidemio-logical literature reviewed in Chapter 6 shows that the elderly are more likely to be prescribed and to use sedative-hypnotic drugs relative to younger age groups.

Two surveys of hypnotic drug usage in residential homes for the elderly, conducted six months apart, are reported in Chapter

7. The drugs and dosages used, and the age, sex, and health status of users are examined. Prospective trends in hypnotic drug prescribing and usage are also considered.

Experiment 2 (Chapter 8) tests the hypothesis that repeated doses of nitrazepam, when used in low (5mg) doses, effectively reduces the probability of daytime performance deficits occurring in the elderly. Experiment 3 (Chapter 9) compares the effects of repeated doses of nitrazepam 5mg and lormetazepam 1.0mg in elderly subjects. An experimental methodology for assessing the pharmacological effects of hypnotic drugs in the elderly is presented.

The results and conclusions are summarized in Chapter 10. Overall, the experimental findings indicate that: 1) in combination, drug elimination half-life and the continuity of drug usage are reliable predictors of daytime behavioural disruption in older age groups; and 2) age related changes increase an individuals vulnerability to such effects. These results are considered in relation to the data from Surveys 1 and 2, and some of the implications are discussed.

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Chapter 8:

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Chapter 1

Introduction

Hypnotics, while being among the most widely prescribed of all drugs (Skegg et al. 1977), are clinically distinct in at least one other important respect. Unlike most other commonly used pharmacological substances, hypnotics are required to act only for a strictly limited period within the 24h cycle. Pharmacological activity which continues to influence behaviour after this period may be considered as a Type A adverse reaction according to the logical schema proposed by Rawlins and Thompson (1977), i.e. a reaction which results from "qualitatively normal, but quantitatively abnormal" pharmacological effects (Rawlins, 1981). Thus, just as sleep cannot be considered apart from wakefulness (a point recently re-emphasized by Dement et al. 1982), so too the actions of hypnotic drugs cannot be considered apart from their implications for daytime behaviour. It is now widely recognized, in both the United Kingdom (Committee on the Review of Medicines, 1980) and the United States (Solomon, 1979: Institute of Medicine Report), that studies of the behavioural consequences of hypnotic drug usage should augment the more traditional clinical attention paid to the efficacy, toxicity, abuse potential, and withdrawal of these products.

The task of detecting and evaluating the daytime consequences of hypnotic drug usage can be approached from several different directions. Controlled clinical observations

of overt CNS depression (e.g. Greenblatt et al. 1977) or an individual's own ratings of daytime drowsiness (see Oswald, 1980) have been successfully employed where sedation is apparent to the clinician, or to the subject, or to both. However, from the earliest laboratory studies of the residual effects of hypnotics (e.g. Walters and Lader, 1971; Bond and Lader, 1972) it is clear that impaired efficiency can be objectively measured in subjects who do not rate themselves as sedated, and who are not overtly drowsy. The objective assessment of performance [performance is defined here as the goal-directed organization of cognitive and motor activities; after Fitts and Posner, 1973], frequently combined with subjective appraisals of mood and feelings, has now become established as the method of choice for evaluating residual sequelae to hypnotic drugs. Such experiments have the potential, not only to indicate the probability of residual side effects occurring following a given hypnotic, but also to specify those skills and aspects of performance most likely to be affected. Unfortunately, while there now exists a considerable literature concerning both the acute and the residual effects of sedative-hypnotic drugs on human performance (for reviews see McNair, 1973; Bixler et al. 1975; Kleinknecht and Donaldson, 1975; Wittenborn, 1979; Hindmarch, 1981; Johnson and Chernik, 1982), in many experiments this potential is far from fully realised.

Successive reviews have pointed out that much of the available experimental data concerning sedative-hypnotic drugs and human performance lack both generality and direct clinical relevance. McNair (1973), for example, reviewing over 100

studies which had investigated the effects of anti-anxiety drugs on performance observed that: "Almost two decades of laissez-faire research in the area have yielded no adequate, systematic data base for meaningful inferences. About all one can safely and tritely conclude is that all these drugs affect performance under some conditions... In view of the widespread use of these drugs and the evidence that impairment and facilitation of performance are often associated with their use, it should be rather startling that we have so little directly relevant clinical information".

A feature of many psychopharmacological studies which particularly limits the generality of data reported (and thus diminishes their clinical relevance) is the unrepresentativeness of subjects. Relatively few studies have employed subjects who typify, in characteristics of age, sex, or health status, the target populations of sedative-hypnotic drugs. McNair (1973), for example, reports that subjects were predominantly healthy male college students; only 12% of all drug-placebo comparisons examined in this review included patient groups. Similarly, in a review of the effects of diazepam on human performance Kleinknecht and Donaldson (1975) found that 79% of all subjects were young healthy males. More recently, Johnson and Chernik (1982), in a detailed review of the effects of sedative-hypnotic drugs on daytime skills have commented: "We note that there are still little data as to the effects of age, sex differences and, as decried in previous reviews, there are far too few performance studies using the medications on the population for which they are intended".

The relevant literature, then, reflects an overall lack of experimental interest in subject-variables which may significantly influence the drug-performance relationship. With particular reference to age, this is a serious omission. A growing body of evidence indicates that metabolic, pharmacokinetic, and pharmacodynamic processes can be greatly affected by physiological changes associated with ageing (James, 1978; Crooks and Stevenson, 1979; Vestal, 1982). With increasing age the response to a given drug may become more profound (Crooks and Stevenson, 1981), and the occurrence of major side effects more frequent (Hurwitz, 1969; Hurwitz and Wade, 1969). Surveys of hospital inpatients, for example, have shown that the frequency of "clinically significant" daytime drowsiness associated with the use of flurazepam (Greenblatt et al. 1977) and nitrazepam (Greenblatt and Allen, 1978) consistently increases with age. Thus, information concerning the daytime behavioural consequences of hypnotic drug usage derived largely from healthy young individuals does not necessarily generalize to older age groups. Clearly, the need exists for detailed, systematic investigations which both acknowledge, and elucidate, the influence of ageing on post- hypnotic behavioural impairments. This need is further emphasized when the prevalence of dissatisfaction with sleep and the consequent use of sedative-hypnotic drugs are also considered in relation to age.

Subjectively estimated sleep quality shows a decline with increasing age (McGhie and Russel, 1962; Kales et al. 1974;

Karacan et al. 1976). Electroencephalographic sleep variables also show age-related trends consonant with these subjective estimates. Total sleep time, and the duration of stages 4 (slow wave sleep) and REM (rapid eye movement) decrease with advancing age, while arousals intervening during sleep become more frequent (Williams et al. 1974; Feinberg, 1976). Thus, sleep becomes progressively less "deep" and more broken. It would also appear that the duration of each intra-sleep arousal tends to be longer in older individuals (Brezinova, 1975). Certainly, estimates of sleep efficiency (as measured by the sleep efficiency index of Total Sleep Time/Total Time in Bed) show a rapid decline between the ages 50y and 79y (e.g. Ø.925 for the age group 5Ø-59y, and Ø.795 for the age group 7Ø-79y; after Williams et al. 1974). These age-related changes in both subjectively assessed and objectively measured sleep have been shown to be correlated with an increase in the use of sedative-hypnotic medications. For example, in a survey of 1654 individuals randomly sampled from an urban community in Florida, USA, Karacan et al. (1976) found that the prevalence of hypnotic drug usage, on at least an occasional basis, increased rapidly during early (4Ø-49y) and late (5Ø-59y) middle age, and continued to increase across the age groups 6Ø-69y and 7Øy+.

Increasing age, therefore, is associated not only with an increased susceptibility to drug side effects, but also with an increased likelihood of receiving certain drugs which produce such reactions. In combination, these clinical and epidemiological findings stress the need for psychopharmacological studies

which recognize age as important, and influential, characteristic of subjects.

The characteristics of experimental subjects are not the only neglected aspects of research concerned with hypnotic drugs and daytime performance. The psychological characteristics of the performance deficit itself have also received scant attention. Broadly, many studies have been concerned only with reporting the presence or absence of residual sequelae to hypnotic drugs. Tests employed for such evaluations tend to be selected, not on the basis of psychological merit or relevance, but are selected rather on the basis of demonstrated or presumed sensitivity to drug effects. Thus, results are frequently reported from test procedures which are not predictive of clinically or psychologically relevant behavioural changes which may follow the use of some hypnotics. Hindmarch (1981), for example, lists over 50 different test procedures which have been used to assess the effects of psychoactive drugs on performance, and has recently concluded that many of these tasks cannot be regarded as "serious attempts at measuring sedation" (Hindmarch, 1982). Statistical analyses, too, infrequently proceed beyond the point at which post-drug behavioural change is established. This approach to the evaluation of residual drug effects has, as McNair (1973) has pointed out, produced an excess of non-cumulative, atheoretical research. Consequently, and despite the sheer volume of reported studies concerned with the residual effects of hypnotics, there exists no comprehensive model which attempts to explain how these drugs may disrupt the organization of human performance. Such a

model can be constructed only from evaluative studies which progress beyond the simple goal of establishing that a given drug, at a given dose, does or does not impair performance on a given task. In both the design and the analysis of the experiments described in this thesis, the need for detailed information on the characteristics of post-drug behavioural change has been recognized.

Organization of Thesis

In the following chapters the residual effects of sedative hypnotics on performance, and the therapeutic usage of these drugs, are considered in relation to age. The intention throughout has been to identify, and respond to, areas of the drug-performance literature where clinically relevant information is particularly lacking. The organization of this thesis reflects these intentions. Several aspects of hypnotic drug use, each pertinent to the issue of daytime behavioural impairment, are individually reviewed and analyzed. Appropriate experimental or epidemiological studies have then been undertaken with the specific aim of testing hypotheses and clarifying assumptions which have direct clinical relevance.

Before presenting the outline of this thesis, brief consideration will be given terminology.

The terms "hypnotic" and "sedative-hypnotic" are used

interchangeably throughout. Where necessary (e.g. Chapter 7), "hypnotic" is operationally defined.

Similarly, the terms "psychotropic", "psychoactive", "behaviourally active", and "psychotherapeutic" (as used in the literature) are treated as synonymous, and refer generically to drugs used to modify mood and behaviour. Hypnotics are subsumed within these categories.

For simplicity, age groups are frequently referred to nominally, rather than numerically. The following classification has been arbitrarily adopted: early middle-age = 40-49y; late middle-age = 50-64y; and "elderly" refers to those aged 65y or more. Numerical categories are used when the age group "elderly" is further sub-divided (e.g. Chapter 7).

Outline of Thesis

Chapter 2 introduces the first experimental study. Information concerning the pharmacology, efficacy, clinical use, and behavioural side effects of two benzodiazepine hypnotics (loprazolam and triazolam) is reviewed, and the age factor is considered. The rationale, design, and execution of the study is then described.

Chapter 3 describes and discusses the effects of loprazolam

and triazolam on the daytime performance efficiency of early and late middle-aged individuals. Characteristics of performance, and of performance-change in the two groups are compared.

Chapter 4 examines the effects of loprazolam and triazolam on subjectively rated mood and daytime feelings, and presents the conclusion to, and implications of, Experiment 1.

Chapter 5 reviews the clinical and experimental data concerning the daytime behavioural consequences of hypnotic drug use in the elderly. Theoretical and practical issues relevant to the cause, and the measurement, of impaired performance in this age group are also considered.

Chapter 6 critically reviews the epidemiological literature concerning hypnotic drug use, and specifically examines the prevalence of hypnotic drug prescribing for the elderly since the early 1960s.

Chapter 7 describes the design and execution of two surveys of hypnotic drug usage in a large elderly population. The information thus provided complements that reviewed in the previous chapter.

Chapter 8 combines information from Chapters 5 and 7 in the design of Experiment 2, which investigates the effects of low-dose nitrazepam on performance in the elderly. This experiment is presented as a pilot study.

Chapter 9 describes Experiment 3, which investigates the effects of nitrazepam and lormetazepam on performance in the elderly. The experimental rationale and testing procedures are derived from both the previous experiment, and from Experiment 1.

Chapter 10 concludes the thesis and considers the clinical, social, and psychological implications of the information presented.

Chapter 2

Experiment 1: A comparison of the effects of two benzodiazepine hypnotics, triazolam and loprazolam, on the daytime performance of middle-aged subjects. Background and Methodology.

Experimental studies indicate that elimination half-life may be a useful predictor of both the occurrence, and the magnitude, of residual sequelae to hypnotic drugs. Nicholson (1981) notes that performance deficits are much less likely to be associated with hypnotics in which the individual elimination half-life does not exceed 24h. Conversely, single clinically-recommended doses of longer acting compounds like nitrazepam and flurazepam have been shown to impair the performance of young volunteers up to 12h after ingestion (Bond and Lader, 1972; Bond and Lader, 1973). While, on experimental grounds, short half-life hypnotics may appear to be devoid of, or associated with lesser residual effects, than some longer acting drugs, the clinical relevance of this conclusion may be limited. A growing literature indicates that both physiological (see Hicks et al. 1981) and behavioural (see Swift, 1982) responses to hypnotic drugs change with advancing age. However, as pointed out in the previous chapter, knowledge of the residual effects of these drugs is derived largely from experiments using young volunteers. Johnson and Chernik (1982), in a review of 52 studies concerned with sedative hypnotics and human performance, found that the bulk of experiments employed subjects aged 18-40y. In contrast, a recent survey of psychotropic drug usage in London (Murray et al. 1981) found that 83% of all hypnotic users were aged 44y or more.

Clearly, the age-range of subject volunteers emerges as an important factor in determining the immediate clinical relevance of experiments measuring the effects of hypnotics on daytime performance.

Impaired performance may arise not only from persistent sedation following single doses of hypnotic drugs, but may also arise from accumulation, either of the drug itself, or of its active metabolites, with repeated doses. Such effects are more likely to be observed under multiple dose experimental conditions which closely simulate the pattern of drug usage encountered in clinical practice. Borland and Nicholson (1975), for example, report that performance impaired 10h after a single (30mg) dose of flurazepam gradually returned to placebo baseline levels by the 19th post-ingestion hour. However, in 10 day (Church and Johnson, 1979) and 16 day (Oswald et al. 1979) periods of repeated daily doses, flurazepam (30mg) has been reported to show a build-up effect, progressively increasing decrements on some tasks. Further, Oswald et al. (1979) report that after three weeks of flurazepam ingestion, significant performance decrements persisted throughout morning, midday, and evening testing sessions. This sustained performance decrement was attributed, in part, to the use of older age-group subjects (mean age = 53y). However, no specific treatment by age interaction analysis was reported.

Multiple dose trials which include periodic testing sessions throughout the day can, then, produce a more realistic profile of a drugs residual influence on behaviour. With particular regard to the timing of test sessions, it is also relevant to note that residual drug effects occur against a background of circadian

variations in the efficiency of human performance. The possibility that drug effects interact with, and may exacerbate, normally occurring troughs in both cognitive (Baddeley et al. 1970) and psychomotor (Colquhoun, 1971) performance efficiency has received little experimental attention. Thus, post-drug testing schedules which include morning, early afternoon, and evening periods can provide information on the time-course of drug effects in relation to known circadian variations in performance. The present experiment is concerned with the effects of two relatively short half-life hypnotics, triazolam, and loprazolam, on daytime performance. The experimental design, subjects, and testing schedule were all selected to optimise both the clinical and psychological relevance of test results.

Triazolam, a benzodiazepine derivative with an elimination half-life estimated to be within the range 2-4h (see Cook, 1980) has been shown to be an effective hypnotic in clinical trials with normal (Wang and Stockdale, 1973) and insomniac (Vogel et al. 1975) volunteers. Over a 28 day period, Reeves (1977) reports continuing hypnotic efficacy for triazolam 0.25mg nightly as subjectively rated by geriatric outpatients (mean age = 68.6y). Experimental studies concerned with the residual effects of single doses of triazolam on daytime performance report equivocal results. In a group of male volunteers aged 21-40y Veldkamp et al. (1974) report that triazolam 0.5 and 1.0mg impaired performance 10h, but not 13h and 16h after ingestion on tests of digit symbol substitution, card-sorting, and occular convergence. Roth et al. (1977), on the other hand, report that performance 10h after triazolam 0.25 and

Ø.5mg did not differ significantly from that 1Øh after placebo on a test battery which included the digit symbol substitution, and card-sorting tasks. Roth et al.'s (1977) experimental group also comprised male adults (n = 12), with ages ranging from 25-35y. In this latter experiment, however, subjects were awakened at 2 a.m. to complete the full test battery (pursuit rotor, Purdue pegboard, continuous arithmetic, digit symbol substitution, and card-sorting), and also to rate their mood on visual analogue scales. As the test battery alone is reported to have taken at least 1hr 15min to complete, then it is likely that placebo scores recorded 1Øh after ingestion (at Ø8.3Ø) were confounded with the effects of grossly disturbed sleep, and do not reflect accurate baseline performance levels. Taking this consideration into account, it cannot be concluded from Roth et al.'s (1977) data that low dose triazolam does not impair early morning performance.

The effects of repeated doses of triazolam on the performance of older subjects has not been experimentally evaluated. Clinical observations, however, have suggested that chronic use of triazolam in doses of Ø.5mg or more can produce a variety of behavioural dysfunctions, including sleep disturbance, acute and chronic anxiety, and paranoid symptoms (van der Kroef, 1979). The emergence of these symptoms, which are reported to subside on withdrawal of the drug, may reflect cumulative drug effects.

Loprazolam (HR 158, Roussel) is a 1-4 benzodiazepine derivative having a mean elimination half-life of 15h (Jochemsen, 1982). In doses of 1-2mg loprazolam has been shown to be an effective

hypnotic in single dose EEG laboratory studies (Oswald et al. 1977), and in repeated dose clinical trials (Petite, 1978). Hindmarch and Clyde (1980) report that two and four consecutive nightly doses of loprazolam (as HR 158) 0.5mg, 1.0mg, and 2.0mg produced no significant residual impairment the following morning on measures of critical flicker fusion, letter cancellation, short term memory, and choice reaction time in 10 healthy young volunteers (mean age = 21.8y). On visual analogue scales, however, these subjects did rate their general performance as impaired following loprazolam 0.5 and 1.0mg, but not following loprazolam 2.0mg. This apparently paradoxical response to the 2.0mg dose is explained by Hindmarch and Clyde (1980) in terms of particularly low placebo baseline scores achieved by subjects in the 2.0mg condition. As with triazolam, loprazolam has not been assessed in multiple dose performance studies using subjects of a clinically representative age group.

A common, and relevant, feature of all the tests cited above showing no residual effects for triazolam and loprazolam is their relatively short duration, most taking less than 10 minutes to complete. Several researchers (Hart et al. 1976; Oswald, 1978; Hindmarch, 1981) have emphasised the advantages of using protracted, low interest tasks to detect residual hypnotic drug effects on behaviour. Hindmarch and Clyde (1980), for example, report a non-significant tendency for loprazolam 2.0mg to increase response latencies in serial subtraction, and attribute this to the low-interest, habitual nature of this task. Insofar as they affect arousal, similarities have been suggested between the

effects of sleep deprivation, and the effects of hypnotic drugs (Hart et al. 1976). According to this rationale, impaired performance following hypnotics may become apparent only after considerable time-on-task, as Wilkinson (1965; 1968) has shown to be the case following sleep deprivation. In experimental practice, tests of vigilance have proved particularly useful in detecting the acute (Hart et al. 1976) and residual (Oswald et al. 1979) effects of benzodiazepine derivatives. Thus, the overall sensitivity of a test battery to residual drugs effects may be enhanced by including measures of the efficiency of sustained attention.

In the present experiment, the effects on daytime performance of triazolam, and loprazolam (as HR 158), were further evaluated, and compared. Specifically, the experimental design required a period of drug taking which would reasonably allow for cumulative effects to emerge and, further, permitted:-

1) the development of such effects, if present, to be assessed throughout the drug taking period; and

2) the time-course of such effects, if present, to be assessed throughout days within the drug taking period.

Also considered in the present study were the effects of drug withdrawal, after sustained usage, on the efficiency of daytime performance. Performance efficiency impaired by hypnotic drug

usage may reasonably be expected to return to normal (baseline) levels on withdrawal of the drug. However, in the short term, drug withdrawal itself can precipitate events which can, in turn, disrupt daytime behaviour. Rebound insomnia, and reduced sleep efficiency (as measured by total sleep time/total time in bed) are well documented features of EEG sleep recordings made immediately after the withdrawal of some hypnotic drugs. Adam et al. (1976), for example, report that following 10 weeks of nitrazepam 5.0mg nightly, intervening wakefulness increased rapidly on withdrawal of the drug, being maximal on the second withdrawal night in a group of 10 middle-aged subjects (mean age = 57y). Similarly, Oswald et al. (1979) report that after three weeks administration of 1mg and 2.5mg doses of the shorter acting benzodiazepine lormetazepam, withdrawal was associated with rebound sleep disturbances which included increases in sleep onset latency (2.5mg) and increased duration of REM periods during the first three hours of sleep (1.0mg) in a group of nine volunteers (mean age = 61y).

Daytime performance may also be disrupted by mood changes produced by drug withdrawal. In particular, subjective feelings of anxiety modified by the use of benzodiazepine hypnotics have been reported to increase above baseline values during the withdrawal period (Allen and Oswald, 1976). The design of the present study, then, further allowed for a detailed assessment of performance efficiency to be made during the immediate withdrawal period.

Methods

Subjects. Twelve volunteers, nine females and three males aged 40-65y (mean age = 52y; median age = 52y), who considered themselves to be poor sleepers, served as subjects. None was receiving psychotropic drugs, and each abstained from alcohol during the experimental periods. Subjects were in good general health, and took part with the consent of their general practitioners. Each subject was paid on completion of the study, and each was reimbursed for travel expenses to and from the laboratory.

Drugs. Subjects received each of the following preparations in identical capsules: triazolam 0.5mg; loprazolam (as HR 158) 1.0mg; loprazolam (as HR 158) 0.5mg; and placebo. Each preparation was taken at the subject's normal bedtime.

Experimental Design. The experimental design is shown diagramatically in Figure 2:1. The basic sequence of weeks shown in this figure will be referred to as an 'experimental period'. Subjects attended the laboratory in groups of six either on Sundays, or on Thursdays. Drugs were administered in a balanced order according to three four-sided Latin squares. Each experimental period lasted six weeks, and was organised as follows: one practice week; one baseline week; three drug/placebo weeks; and one withdrawal week (see Fig 2:1). Experimental periods were separated by four-week washout periods, during which the subjects took no capsules, and the experimental constraints on

Figure 2:1 The Study Design

Subjective Ratings	←							→
Treatment	Placebo		Placebo	Placebo	Drug or Placebo	Drug or Placebo	Drug or Placebo	Placebo
Week of Study	Adaptation*		Practice	Baseline	Week 1	Week 2	Week 3	Withdrawal
	1		1	8	15	22	29	36 43
Day of Study	3		3	10	17	24	31	38
Performance Testing	Test		Test	Test	Test	Test	Test	Test

* beginning of study only

Treatments commenced at bedtime on Day 1.

The above sequence (excluding the adaptation week) was repeated on 3 further occasions.

alcohol consumption did not apply. For all subjects, a single adaptation week, during which they took placebo capsules and attended the laboratory for testing, preceded, and was continuous with, their first treatment condition. Thus, each subject participated for a total of 37 weeks (experimental periods + washout periods). Subjects were blind to all conditions, including the preliminary adaptation week. The experimenter was blind only to the three drug/placebo weeks in each treatment condition.

Test Schedule

All testing procedures were conducted in the performance laboratory. Subjects attended the laboratory on the morning following the second night of capsule ingestion, and thereafter on the same day at weekly intervals (see Figure 2:1). Thus, for the first experimental period subjects attended the laboratory on seven testing days, and for each of the remaining three experimental periods, subjects attended on six testing days. For each of these days of attendance the test procedures, which took approximately 2h to complete, were administered at three times throughout the day commencing at 08.30, 12.30, and 16.30. The tests, in their order of administration, were as follows:

1) the Wilkinson Auditory Vigilance Test (Wilkinson, 1970). For 1h the subjects listened through headphones to a series of standard 1000Hz tones of 0.5sec duration which were presented every 2sec. Tones were of 60dB intensity, and each occurred against a background

of 70dB continuous white noise. Target signals were tones of 0.4sec instead of the 0.5sec standard. The ratio of target signals to standard tones was 1-48. Target signals were presented according to six 10min semi-random distributions which ran continuously during the one hour period. The order in which these 10min distributions were presented was varied on each testing occasion. Subjects sat in individual cubicles and were required to register their detection of a target signal by pushing a button. Watches were left outside the cubicle. For each of the six continuously running target signal distributions, both correct detections and false reports (i.e. registering a detection after a standard tone) were recorded. No feedback to subjects (i.e. no knowledge of results) was given.

2) Manual Dexterity. Subjects were required to place cylindrical pellets 5.5mm in diameter into an upright tube of slightly larger bore. The tube, mounted on a collecting chamber, was placed directly in front of each seated subject within the testing cubicles. Pellets would enter in only one orientation, viz. perpendicular to the tube. Subjects were required to place into the tube as many pellets as possible, using the preferred hand, picking up only one pellet at a time. A single trial lasted one minute, and was followed by a one minute inter-trial interval. Six trials were repeated in identical manner. During the inter-trial interval, subjects emptied the collecting chamber and recorded the number of pellets placed in that trial. The results from trials 2-5 only were recorded for subsequent analysis. Trial 1 was considered a practice or 'adaptation' trial, and

final trials in a series, in this case, trial 6, are known to be influenced by "end spurt" accelerations in performance (Catalano, 1973).

3) The Digit Symbol Substitution Test. Using a modified version of the Wechsler Adult Intelligence Scale coding sub-test (Wechsler, 1958), subjects were required to enter digits below corresponding symbols according to a given code. Eight different symbols were randomly arranged in printed blocks of 200. Two such blocks were provided, the code being printed above the first block (see appendix 1:1). Two minutes were allowed for coding, the subject being asked to work as quickly and as accurately as possible. Nine different translation codes were randomly varied throughout the experiment to offset possible learning effects. The total number of items correctly coded, and the total number of items incorrectly coded, were recorded for each session.

4) The Crossman Card-Sorting Task (Crossman, 1953). Packs of 32 ordinary playing cards were sorted on a specially constructed tray (55cm x 48cm) divided into two rows of four 1cm deep compartments (15cm x 10cm). The pack was placed in a three-sided compartment, also 1cm deep, which was centrally situated on the side of the tray nearest the subject, and from which single cards could be drawn from the top of the pack with one hand. Three packs of 32 cards were used for sorting: a two-category pack containing equal numbers of 2s and 3s; a four-category pack containing equal

numbers of 2s, 3s, 4s, and 5s, and an eight-category pack containing equal numbers of 2s, 3s, 4s, 5s, 6s, 7s, 8s and 9s. Fixed face-up to the bottom of each of the eight sorting compartments was an example of each of these denominations, a 2, 3, 4, and 5, from left to right across the top row, and a 6, 7, 8, and 9, from left to right across the bottom row. A further pack of 32 cards, the movement-time pack, contained only 1Øs. For each subject, the four packs, and the eight example cards, were of the same colour.

Trials commenced with the movement-time pack of cards being placed face-down in the open ended compartment. The subject was first asked to place, one at a time, cards from this pack into the "2" and "3" compartments, sharing the pack equally between the two. This procedure was then repeated for compartments 2-5, and 2-9. The sequence was then reversed, and the subject shared the pack equally between compartments 2-9, then 2-5, and finally 2-3. The subject was then presented with the two-category pack, and asked to sort each card into its matching compartment. This was repeated for the four-category pack, and then the eight-category pack. The order was then reversed, and the subject then sorted the eight-, four-, and two-category packs. For each movement-time and sorting trial, the subject was asked to work as quickly, and as accurately as possible. Each sorting pack was shuffled before use. The timing of each trial commenced with the verbal cue "go", and stopped when the final card from the pack was placed. The mean of each pair of two-, four-, and eight-category movement times, and two-, four-, and eight-category sorting times were

recorded. The movement time was then deducted from the approprate sorting time (e.g. two-category sorting time minus the two-category movement time) and the resulting Choice Reaction Time (Crossman, 1953) was also recorded for analysis.

Subjective Ratings

Throughout each of the experimental periods subjects rated their mood and behaviour using visual analogue scales. These instruments, their analysis, and the results, are fully described in Chapter 4.

Analysis of Data

Test scores from the baseline weeks, the drug/placebo weeks, and the withdrawal weeks only were used in the analysis. To reduce the impact of initial baseline group differences on the subsequent analyses of performance change, unweighted deviation scores were calculated. For a full discussion of the statistical reliability of such indices of change, see Overall (1977). Within each of the four experimental periods, deviation scores were calculated by deducting each of a given subject's drug/placebo week scores, and withdrawal week scores, from that subject's appropriate baseline week score (e.g. Ø8.3Ø baseline score minus

Ø8.3Ø week 1 score, etc.). Deviation scores were derived for each occasion of testing throughout the drug/placebo and withdrawal weeks for each drug treatment. Scores from the drug/placebo weeks, and scores from the withdrawal week, were analyzed separately.

For each test measurement, deviation scores from the drug/placebo weeks were analyzed using a repeated measures analysis of variance model (Jenrich and Sampson, 1979) with three trial factors (drug, week, and time), and one grouping factor (age). Levels for each of the trial factors were as follows. Drug: (1) triazolam Ø.5mg; (2) loprazolam 1.Ømg; (3) loprazolam Ø.5mg; (4) placebo. Week: (1) week 1 testing sessions; (2) week 2 testing sessions; (3) week 3 testing sessions. Time (1) Ø8.3Ø testing sessions; (2) 12.3Ø testing sessions; (3) 16.3Ø testing sessions. The grouping factor, age, which was crossed with each of the trial factors had two levels: (1) those subjects above the group median age at the start of the experiment; (2) those subjects below the group median age at the start of the experiment.

The main effects of, and interactions between these factors were computed. Where significant main effects of the drug factor were found, within-factor means were compared using correlated t-tests. Significant interactions between the drug factor and the 'test occasions' factors (i.e. week, time, or week x time) were further evaluated by repeating the analysis of variance for each separate week, or each separate time as appropriate to determine

the influence of drug on these occasions of testing. Where significant four-way interactions were found (i.e. drug x week x time x age) the analysis was repeated for each separate time of day to determine the combined influence of drug and age on weekly test performance. Where appropriate, treatment means from significant drug x age interactions were compared using correlated t-tests. Similarly, and where appropriate, treatment means from significant drug x test occasions factors were also compared using correlated t-tests. These latter comparisons were undertaken only where they assisted in the interpretation of significant interactions.

Scores from the withdrawal period were separately analyzed by repeated measures analysis of variance with two trial factors (drug and time) and one grouping factor (age). Levels for these factors were as described above. Main effects of, and interactions between these factors were also similarly evaluated.

Two-tailed tests of significance were used throughout. The results of these analyses are presented and discussed in the next chapter.

Chapter 3

Experiment 1: Effects of triazolam and lormetazepam on the daytime performance of middle-aged subjects.

The effects of the four experimental treatments (viz. placebo, loprazolam 1.0mg, triazolam 0.5mg, and loprazolam 0.5mg) on performance in weeks 1, 2, and 3 (the drug/placebo weeks) are summarized in Table 3:1. Complete analysis of variance tables for each variable are shown in Appendix 2. These results, and the results of further analyses, will be considered for each test in turn. With the single exception of false positive reports on the auditory vigilance test, all results refer to deviation scores, calculated as described above. In both the figures and tables presented in this chapter, the following abbreviations have been adopted: P (placebo); T (triazolam 0.5mg); L1.0 (loprazolam 1.0mg); and L0.5 (loprazolam 0.5mg). Also, the two groups created by the age factor in the analyses of variance will be referred to as the older sub-group, and the younger sub-group (i.e. older and younger than the group median age).

Results

This section describes the results from the main analyses, and indicates where further analyses were undertaken; it also provides a guide to the Figures and Tables. All the results are fully discussed in the next section.

Table 3:1 Summary of results from main analyses of variance (F values)

Test/Variable	Main Effects	Interaction Effects						
	Drug	D A	D W	D T	D W A	D T A	D W T	D W T A
Auditory Vigilance								
% detections (1 hour)	0.60	0.17	0.45	0.62	1.10	1.97	1.06	1.77
% detections (final 40 min)	3.30*	0.82	0.47	0.82	0.90	1.14	0.90	2.13*
false reports (1 hour)	1.07	1.98	1.22	1.16	1.54	2.28*	0.68	2.24*
Digit Symbol Substitution	1.38	0.33	1.69	0.75	0.14	0.46	0.55	1.16
Card Sorting:								
movement time (2 category)	1.37	1.97	0.26	0.68	0.72	1.33	2.03*	0.87
movement time (4 category)	1.89	1.31	0.63	0.56	0.42	0.74	0.57	1.26
movement time (8 category)	1.67	3.20*	0.83	2.78*	0.49	0.29	0.95	0.52
Choice Reaction Time								
(2 category)	1.80	1.19	0.50	2.51*	0.99	2.04	1.47	1.20
(4 category)	2.26	2.59	0.76	1.15	0.22	0.47	1.58	2.32*
(8 category)	1.24	0.38	0.39	0.73	0.24	0.95	1.66	1.30
Manual Dexterity	0.97	0.93	0.60	2.28*	1.40	1.25	0.64	2.13*

D = Drug (treatment)
A = Age (grouping)
W = Week (of testing)
T = Time (of day)

* $p<0.05$
** $p<0.01$

Auditory Vigilance

Correct detections were converted to percentages of the total number of target signals presented prior to the computation of deviation scores. Percent correct detections over 1h showed no main effect of drug, and no significant interaction effects between drug and age, or between drug and either of the test occasions factors (Table 3:1). Percent correct detections for the final 40min of the test, however, showed a significant main drug effect ($F = 3.30$, $df = 3,30$, $p<0.05$), and also showed a significant drug x week x time x age interaction ($F = 2.13$, $df = 12,120$, $p<0.05$). The significant main effect of drug was further evaluated by multiple comparisons of the cell means for each drug condition using correlated t-tests. The results from these comparisons, together with the drug treatment means, are shown in Table 3:2. To further evaluate the significant 4-way interaction, the analysis of variance was repeated for each time of day (i.e. the analysis was repeated with time held constant). The results of these further analyses of the 08.30, 12.30, and 16.30 testing sessions are shown in Figures 3:2a, 3:2b, and 3:2c respectively. Separate analyses of the 12.30 (Figure 3:2b) and 16.30 (Figure 3:2c) times of testing showed no significant main effects of drug, and no significant interaction effects between drug and age, or between drug and weeks. However, separate analysis of percent correct detections for the final 40min of the auditory vigilance test recorded at the 08.30 test sessions (Figure 3:2a) showed a significant drug x week x age interaction ($F = 3.11$, $df = 6.60$,

Table 3:2 Auditory vigilance: paired comparisons between treatment means for correct detections (final 40min)

Drug Treatment (Mean; SD)	Placebo (2.0%; 8.47)	Loprazolam 1.0	Triazolam 0.5
Loprazolam 1.0 (-3.6%; 10.10)	t = 1.11	-	-
Triazolam 0.5 (1.39%; 7.19)	t = 0.27	t = 1.29	-
Loprazolam 0.5 (-6.04%; 9.33)	t = 2.43*	t = 1.62	t = 2.37*

* $p<0.05$
** $p<0.01$

Values are shown for t (correlated)

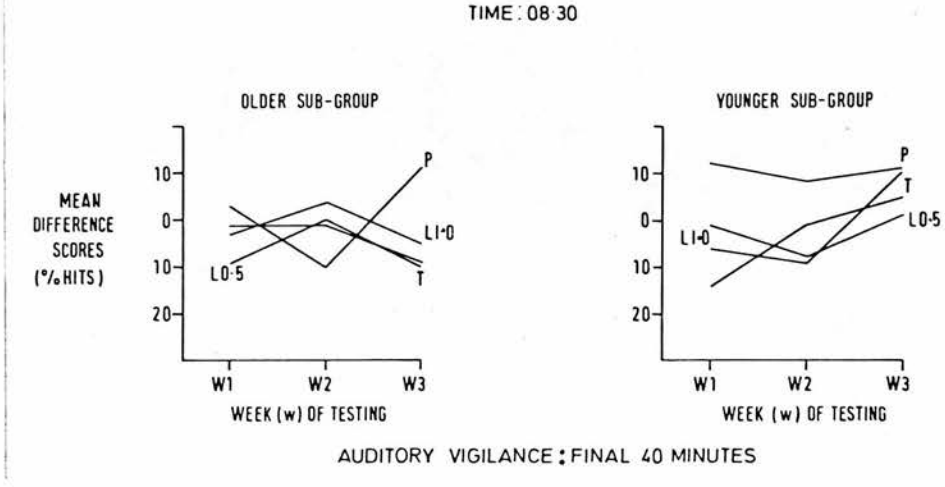


Figure 3:2a Effects of two hypnotics on auditory vigilance performance at 08.30

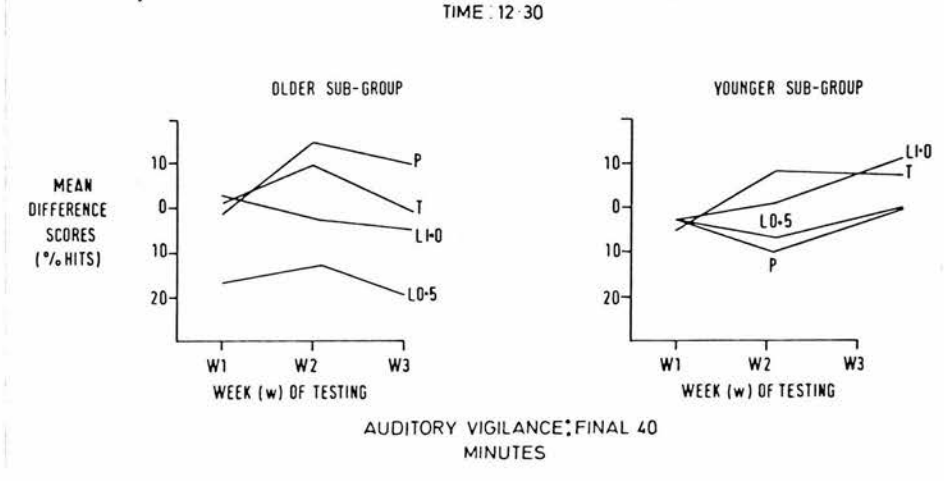


Figure 3:2b Effects of two hypnotics on auditory vigilance performance at 12.30

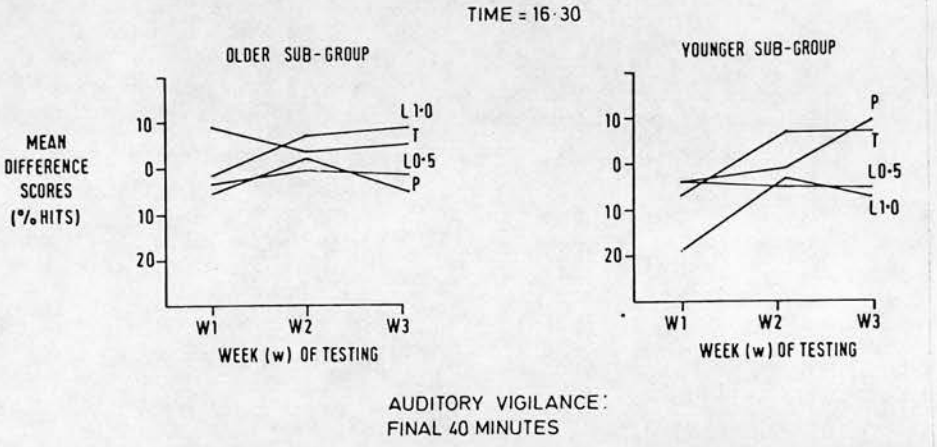


Figure 3:2c Effects of two hypnotics on auditory vigilance performance at 16.30

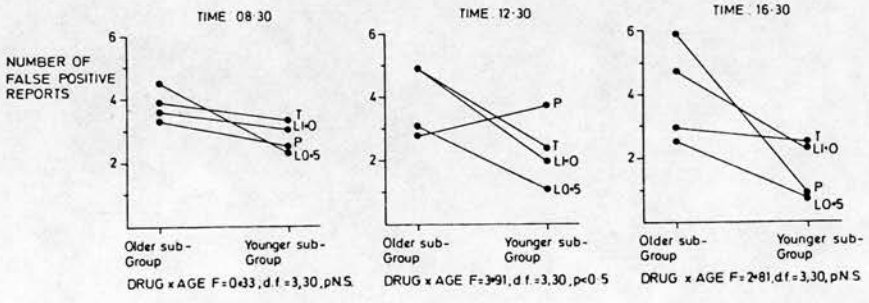


Figure 3:3 Effects of two hypnotics on false positive reporting in two age groups

Table 3:3 Paired comparisons between treatment conditions for correct detections (final 40min) on the auditory vigilance task

	Older Sub-group			Younger Sub-group			
Drug	P	L1.Ø	T	P	L1.Ø	T	Time
			Week 1				
L1.Ø	Ø.42	-	-	2.13	-	-	
T	Ø.47	Ø.Ø3	-	1.85	Ø.61	-	Ø8.3Ø
LØ.5	1.67	Ø.95	1.21	2.19	Ø.64	1.42	
L1.Ø	Ø.69	-	-	Ø.ØØ	-	-	
T	Ø.57	Ø.29	-	Ø.17	Ø.2Ø	-	12.3Ø
LØ.5	Ø.77	1.32	1.18	Ø.Ø4	Ø.Ø5	Ø.17	
L1.Ø	Ø.29	-	-	1.Ø3	-	-	
T	1.75	1.Ø5	-	Ø.42	1.Ø5	-	16.3Ø
LØ.5	Ø.41	Ø.19	1.49	Ø.Ø6	1.16	Ø.91	
			Week 2				
L1.Ø	1.4Ø	-	-	1.21	-	-	
T	1.73	Ø.41	-	Ø.84	1.67	-	Ø8.3Ø
LØ.5	1.24	Ø.56	Ø.Ø2	1.54	Ø.15	Ø.79	
L1.Ø	1.88	-	-	1.19	-	-	
T	Ø.28	1.Ø1	-	2.22	Ø.82	-	12.3Ø
LØ.5	1.69	Ø.94	1.9Ø	Ø.69	1.32	2.64*	
L1.Ø	Ø.49	-	-	Ø.32	-	-	
T	Ø.16	Ø.4Ø	-	Ø.52	Ø.53	-	16.3Ø
LØ.5	Ø.76	Ø.91	Ø.51	Ø.28	Ø.Ø8	2.77*	
			Week 3				
L1.Ø	Ø.91	-	-	Ø.14	-	-	
T	1.82	Ø.21	-	Ø.33	Ø.61	-	Ø8.3Ø
LØ.5	1.4Ø	Ø.29	Ø.21	1.32	Ø.92	Ø.33	
L1.Ø	1.15	-	-	1.14	-	-	
T	Ø.94	Ø.83	-	1.Ø3	Ø.25	-	12.3Ø
LØ.5	2.19	1.96	2.Ø5	Ø.Ø2	1.15	Ø.71	
L1.Ø	1.82	-	-	1.95	-	-	
T	1.25	Ø.27	-	Ø.53	2.31	-	16.3Ø
LØ.5	Ø.63	Ø.8Ø	Ø.54	1.41	Ø.24	1.39	

* $p<Ø.Ø5$
** $p<Ø.Ø1$

Values shown are for t (correlated), df = 5, two-tailed probablities

p<Ø.Ø1). Within each sub-group, and for each week of testing, paired comparisons between the drug conditions for the Ø8.3Ø, 12.3Ø, and 16.3Ø test sessions are shown in Table 3:3.

Analysis of the absolute number of false reports over 1h showed no significant main effect of drug, but did show significant drug x time x age (F = 2.28, df = 6,6Ø, P<Ø.Ø5) and drug x week x time x age (F = 2.24, df =12,12o, p<Ø.Ø1) interactions. Both of these significant interactions were further evaluated by repeating the analysis of variance for the Ø8.3Ø, 12.3Ø, and 16.3Ø testing sessions. The combined influence of drug and age on false positive reports is shown in Figure 3:3. The combined influence of drug, age, and week on false positive reports is shown in Figures 3:4a, 3:4b, and 3:4c for the Ø8.3Ø, 12.3Ø and 16.3Ø test sessions respectively. At the Ø8.3Ø (figure 3:4a) test sessions, false reports showed no sigificant main effect of drug, and no significant interaction effects between drug and age, or between drug and weeks. Separate analysis of the 12.3Ø test sessions (Figure 3:4b) showed a significant drug x age interaction (F = 3.91, df = 3,3Ø, p<Ø.Ø5). For the 16.3Ø test sessions (Figure 3:4b) a highly significant interaction was found between drug, week, and age (F = 3.38, df = 6,6Ø, p<Ø.Ø1). Within each sub-group, and for each week of testing paired comparisons between the drug conditions for the Ø8.3Ø, 12.3Ø, and 16.3Ø test sessions are shown in Table 3:4.

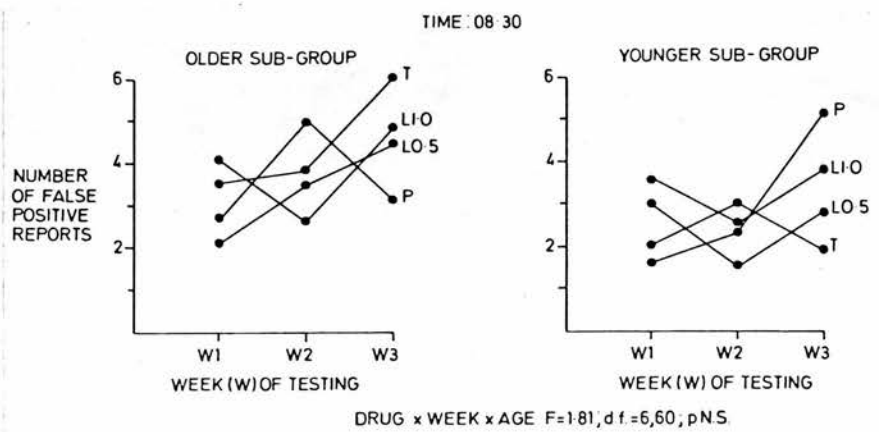


Figure 3:4a Effects of two hypnotics on false positive reporting by time and age

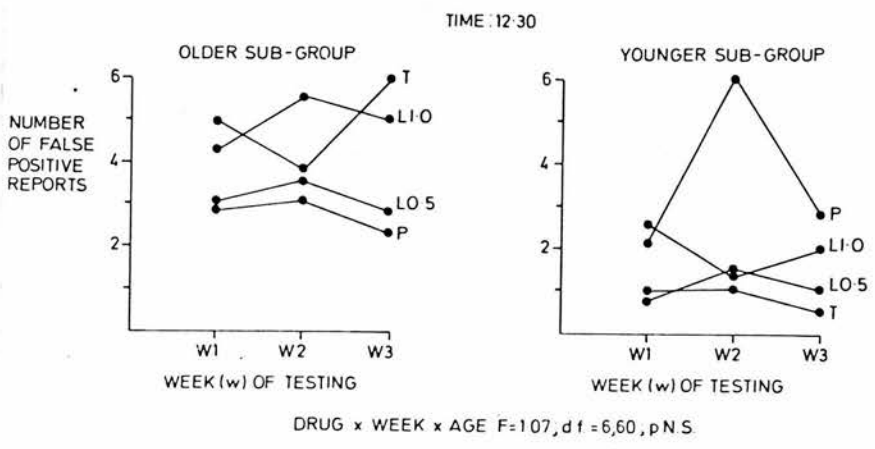


Figure 3:4b Effects of two hypnotics on false reporting by time and age

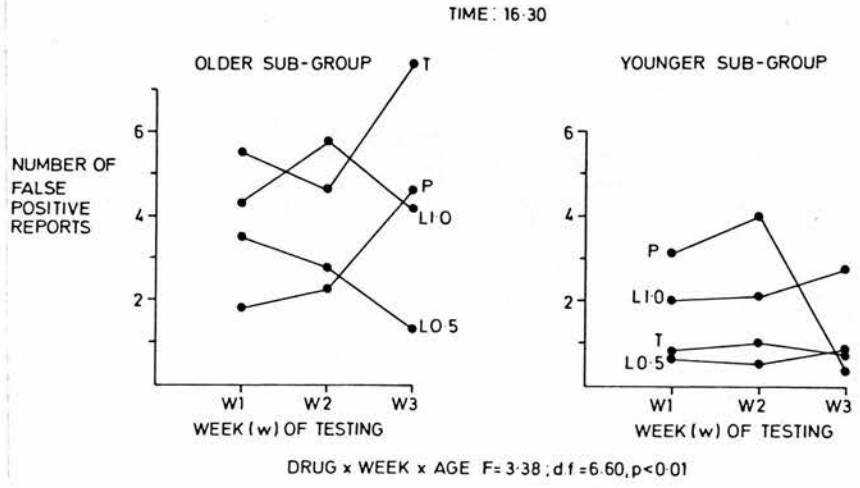


Figure 3:4c Effects of two hypnotics on false positive reporting by time and age

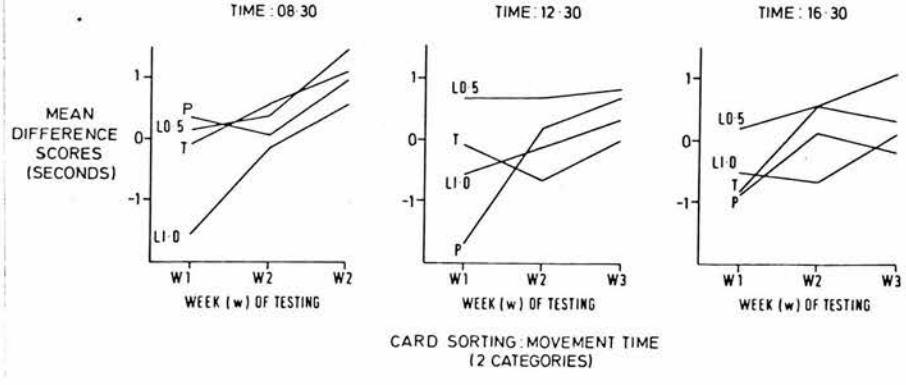


Figure 3:5 Effects of two hypnotics on movement time (card sorting) by time of day

Table 3:4 Paired comparisons between treatment conditions for false positive reports on the auditory vigilance task

	Older sub-group			Younger sub-group			
Drug	P	Ll.Ø	T	P	Ll.Ø	T	Time
			Week 1				
Ll.Ø	Ø.67	-	-	Ø.82	-	-	
T	1.11	Ø.35	-	Ø.19	1.46	-	Ø8.3Ø
LØ.5	Ø.5Ø	1.41	2.39	Ø.53	Ø.21	Ø.43	
Ll.Ø	Ø.61	-	-	Ø.33	-	-	
T	1.43	Ø.32	-	Ø.93	Ø.93	-	12.3Ø
LØ.5	Ø.19	Ø.57	1.41	1.35	1.1Ø	Ø.2Ø	
Ll.Ø	1.42	-	-	Ø.79	-	-	
T	1.87	Ø.49	-	1.63	1.94	-	16.3Ø
LØ.5	1.69	Ø.47	1.49	1.73	1.57	Ø.79	
			Week 2				
Ll.Ø	1.26	-	-	Ø.15	-	-	
T	1.19	Ø.16	-	Ø.47	Ø.25	-	Ø8.3Ø
LØ.5	1.38	Ø.45	Ø.4Ø	1.Ø5	Ø.71	1.77	
Ll.Ø	1.66	-	-	2.87*	-	-	
T	Ø.44	Ø.91	-	2.13	Ø.19	-	12.3Ø
LØ.5	Ø.47	1.15	Ø.Ø8	2.49*	Ø.18	Ø.31	
Ll.Ø	3.13*	-	-	Ø.7Ø	-	-	
T	1.94	Ø.66	-	1.Ø9	2.15	-	16.3Ø
LØ.5	Ø.54	1.96	3.Ø5*	1.35	2.99*	2.24	
			Week 3				
Ll.Ø	1.3Ø	-	-	Ø.5Ø	-	-	
T	1.43	Ø.74	-	1.36	1.31	-	Ø8.3Ø
LØ.5	Ø.72	Ø.21	Ø.81	Ø.92	Ø.68	2.24	
Ll.Ø	2.22	-	-	Ø.64	-	-	
T	1.53	Ø.74	-	2.Ø9	2.24	-	12.3Ø
LØ.5	Ø.89	1.9Ø	1.24	1.87	Ø.81	Ø.65	
Ll.Ø	Ø.45	-	-	1.45	-	-	
T	1.63	1.58	-	Ø.6Ø	1.19	-	16.3Ø
LØ.5	2.45*	1.68	4.66**	Ø.75	1.Ø8	Ø.54	

* $p<Ø.Ø5$
** $p<Ø.Ø1$

Values shown are for t (correlated), df = 5, two-tailed probablities

Digit Symbol Substitution

Analysis of variance of the digit symbol substitution test data (items correctly coded) showed no significant main effect of drug, and no significant interaction effects between drug and age, or between drug and either of the test occasions factors (Table 3:1). Errors (i.e. items incorrectly coded) occurred with an extremely low frequency throughout the experiment under all treatment conditions, providing insufficient data for analysis.

Card Sorting

Movement time from the two-category condition of the card sorting task showed no significant main effect of drug, but did show a significant drug x week x time interaction effect ($F = 2.03$, $df = 12,120$, $p<0.05$). The analysis of these data was, therefore, repeated for each time of testing separately to determine the influence of drug treatment and week at the 08.30, 12.30, and 16.30 times of testing. The results of these analyses are shown in Figure 3:5. None of these further analyses showed significant main effects of drug, or showed significant interaction effects between drug and week. For each week of testing, paired comparisons between the drug conditions for the 08.30, 12.30, and 16.30 test sessions are shown in Table 3:5.

The four-category movement times showed no significant main effect of drug, and no significant interactions between drug and

Table 3:5 Movement time (two category) from the card sorting task: paired comparisons between drug conditions for each week, and for each time of testing

	Week 1 Testing Sessions			
Drug (mean; SD)	P(Ø.37; 1.98)	L1.Ø	T	Time
L1.Ø (-1.58; 2.68)	2.13*	-	-	Ø8.3Ø
T (-Ø.12; 2.84)	Ø.39	1.14	-	
LØ.5 (Ø.13; 1.78)	Ø.33	1.99	Ø.25	
	P(-1.72; 4.2Ø)	L1.Ø	T	12.3Ø
L1.Ø (-Ø.55; 1.8Ø)	Ø.89	-	-	
T (-Ø.1Ø; 2.19)	1.17	Ø.52	-	
LØ.5 (Ø.67; 1.38)	1.9Ø	1.75	1.Ø4	
	P(-Ø.9Ø; 1.42)	L1.Ø	T	16.3Ø
L1.Ø (-Ø.53; 1.54)	Ø.56	-	-	
T (-Ø.8Ø; 1.49)	Ø.14	Ø.35	-	
LØ.5 (Ø.18; 1.34)	1.9Ø	1.Ø1	2.15*	
	Week 2 Testing Sessions			
	P(Ø.Ø6; 1.82)	L1.Ø	T	Ø8.3Ø
L1.Ø (-Ø.22; 1.42)	Ø.59	-	-	
T (Ø.71; 2.81)	Ø.84	1.Ø5	-	
LØ.5 (Ø.39; 1.75)	Ø.51	Ø.84	Ø.37	
	P (Ø.18; 1.9Ø)	L1.Ø	T	12.3Ø
L1.Ø (-Ø.17; 2.14)	Ø.43	-	-	
T (-Ø.67; 3.3Ø)	Ø.63	Ø.55	-	
LØ.5 (Ø.67; 1.71)	Ø.73	1.58	1.23	
	P(Ø.25; 1.59)	L1.Ø	T	16.3Ø
L1.Ø (-Ø.68; 1.62)	1.52	-	-	
T (Ø.54; 1.79)	Ø.5Ø	1.44	-	
LØ.5 (Ø.59; 1.49)	Ø.64	2.12*	Ø.1Ø	

(continued over)

Table 3:5 (continued)

	Week 3 Testing Sessions			
	P(Ø.93; 1.74)	L1.Ø	T	Ø8.3Ø
L1.Ø (Ø.56; 1.77)	Ø.6Ø	-	-	
T (1.11; 2.26)	Ø.18	Ø.68	-	
LØ.5 (1.5Ø; 2.14)	Ø.91	1.Ø6	Ø.41	
	P(Ø.66; 2.35)	L1.Ø	T	12.3Ø
L1.Ø (Ø.3Ø; 2.22)	Ø.39	-	-	
T (-Ø.4Ø; 1.66)	Ø.75	Ø.49	-	
LØ.5 (Ø.8Ø; 2.31)	Ø.13	Ø.58	1.Ø3	
	P(-Ø.17; 1.91)	L1.Ø	T	16.3Ø
L1.Ø (Ø.11; 1.99)	Ø.46	-	-	
T (Ø.32; 1.7Ø)	Ø.73	Ø.3Ø	-	
LØ.5 (Ø.98; 1.55)	1.68	1.45	1.ØØ	

Values shown between conditions are for t (correlated)

Table 3:6a Movement time (eight category) from the card sorting task: paired comparisons between the drug treatment means within the older, and the younger sub-groups

Older sub-group

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L1.Ø (-Ø.38; Ø.92)		P (-Ø.17; 1.Ø6)	Ø.41
T (1.Ø7; 1.62)		P (-Ø.17; 1.Ø6)	1.66
LØ.5 (Ø.52; Ø.58)		P (-Ø.17; 1.Ø6)	1.6Ø
L1.Ø (-Ø.38; Ø.92)		T (1.Ø7; 1.62)	1.97
L1.Ø (-Ø.38; Ø.92)		LØ.5 (Ø.52; Ø.58)	1.98
T (1.Ø7; 1.62)		LØ.5 (Ø.52; Ø.58)	1.35

Younger sub-group

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L1.Ø (-Ø.34; 1.5Ø)		P (Ø.84; Ø.55)	1.91
T (-Ø.25; Ø.71)		P (Ø.84; Ø.55)	3.Ø5*
LØ.5 (-Ø.Ø3; Ø.94)		P (Ø.84; Ø.55)	2.28
L1.Ø (-Ø.34; 1.5Ø)		T (-Ø.25; Ø.71)	Ø.18
L1.Ø (-Ø.34; 1.5Ø)		LØ.5 (-Ø.Ø3; Ø.94)	Ø.44
T (-Ø.25; Ø.71)		LØ.5 (-Ø.Ø3; Ø.94)	Ø.48

* p<Ø.Ø5 ** p<Ø.Ø1

age, or between drug and either of the test occasions factors (Table 3:1).

Analysis of variance of the eight-category movement times also showed no significant main effect of drug, but did show significant interaction effects between drug treatment and age ($F = 3.20$, $df = 3,30$, $p<0.05$), and between drug treatment and time of testing ($F = 2.78$, $df = 6,60$, $p<0.05$). These two-way interactions are shown in Figures 3:6 and 3:7 respectively. Paired comparisons between the drug treatment means within each sub-group, and also between the drug condition means for each time of testing, are shown in Table 3:6a and 3:6b respectively.

Choice reaction time in the two-category condition showed no main effect of drug, but did show a significant interaction effect between drug condition and time of testing ($F = 2.51$, $df = 6,60$, $p<0.05$). This two-way interaction is shown in Figure 3:8, and the cell means for each drug condition, at each of the three times of testing, are compared in Table 3:7.

In the four-category condition of the choice reaction time task, analysis of variance showed no significant main effect of drug, but did show a significant reaction between drug, week, time, and age ($F = 2.23$, $df = 11,120$, $p<0.01$). The analysis of these data was then repeated for each separate time of testing, and these results are shown in Figures 3:9a, 3:9b, and 3:9c for the 08.30, 12.30, and 16.30 times of testing respectively. Separate analysis of variance of the 08.30 and 16.30 test session data showed no

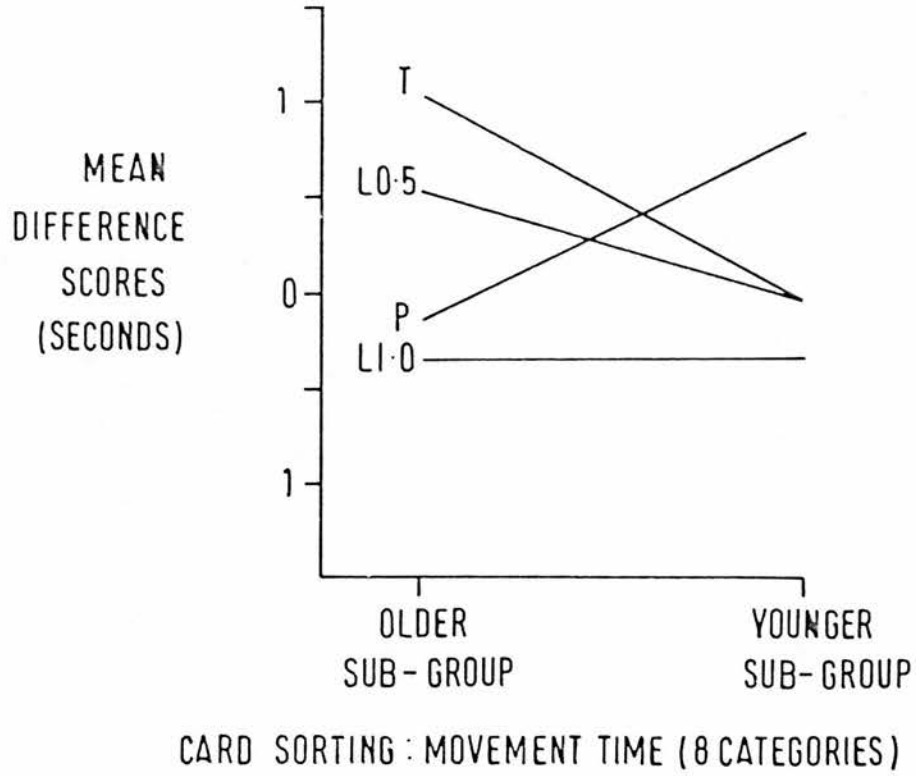


Figure 3:6 Effects of two hypnotics on movement time (card sorting) by age group

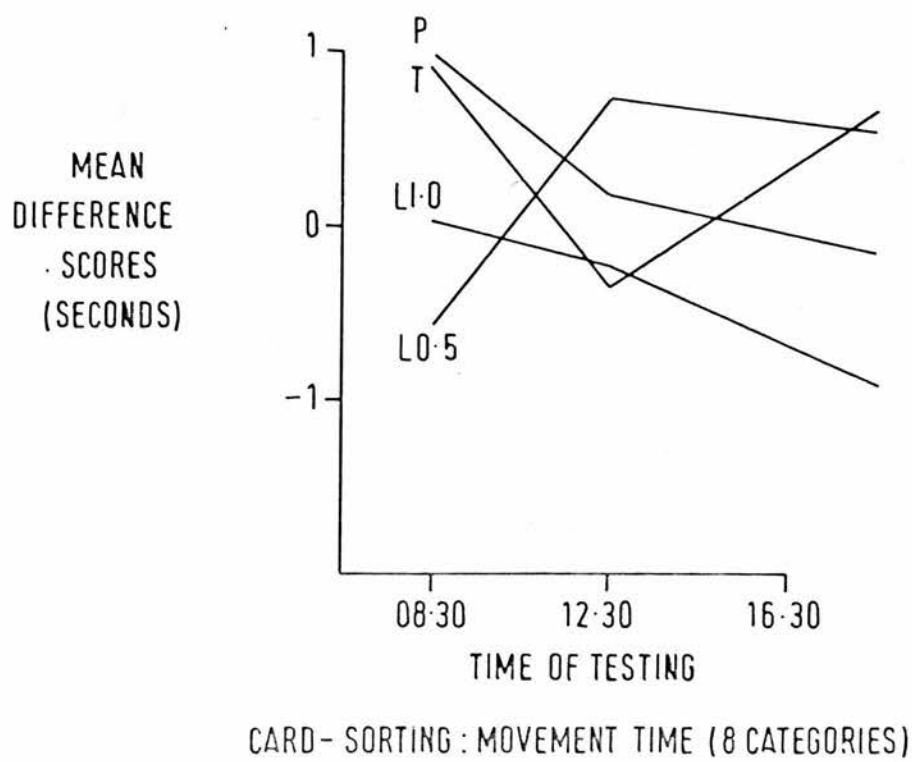


Figure 3:7 Effects of two hypnotics on movement time (card sorting) by time of day

Table 3:6b Movement time (eight category) from the card sorting task: paired comparisons between the drug treatment means for each time of testing

08.30 Testing Sessions

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L1.0 (0.02; 1.83)		P (1.00; 1.70)	1.36
T (0.93; 1.33)		P (1.00; 1.70)	0.09
L0.5 (-0.54; 1.18)		P (1.00; 1.70)	2.25*
L1.0 (0.02; 1.83)		T (0.93; 1.33)	1.17
L1.0 (0.02; 1.83)		L0.5 (-0.54; 1.18)	0.75
T (0.93; 1.33)		L0.5 (-0.54; 1.18)	4.19**

12.30 Testing Sessions

L1.0 (-0.21; 1.58)		P (0.16; 1.78)	0.86
T (-0.36; 1.64)		P (0.16; 1.78)	0.67
L0.5 (0.73; 1.47)		P (0.16; 1.78)	0.91
L1.0 (-0.21; 1.58)		T (-0.36; 1.64)	0.24
L1.0 (-0.21; 1.58)		L0.5 (0.73; 1.47)	1.85
T (0.36; 1.64)		L0.5 (0.73; 1.47)	1.89

16.30 Testing Sessions

L1.0 (-0.90; 1.31)		P (-0.15; 1.27)	1.59
T (0.67; 1.61)		P (-0.15; 1.27)	1.12
L0.5 (0.56; 1.74)		P (-0.15; 1.27)	1.20
L1.0 (-0.90; 1.31)		T (0.67; 1.61)	2.57*
L1.0 (-0.90; 1.31)		L0.5 (0.56; 1.74)	2.42*
T (0.67; 1.61)		L0.5 (0.56; 1.74)	0.23

* $p<0.05$
** $p<0.01$

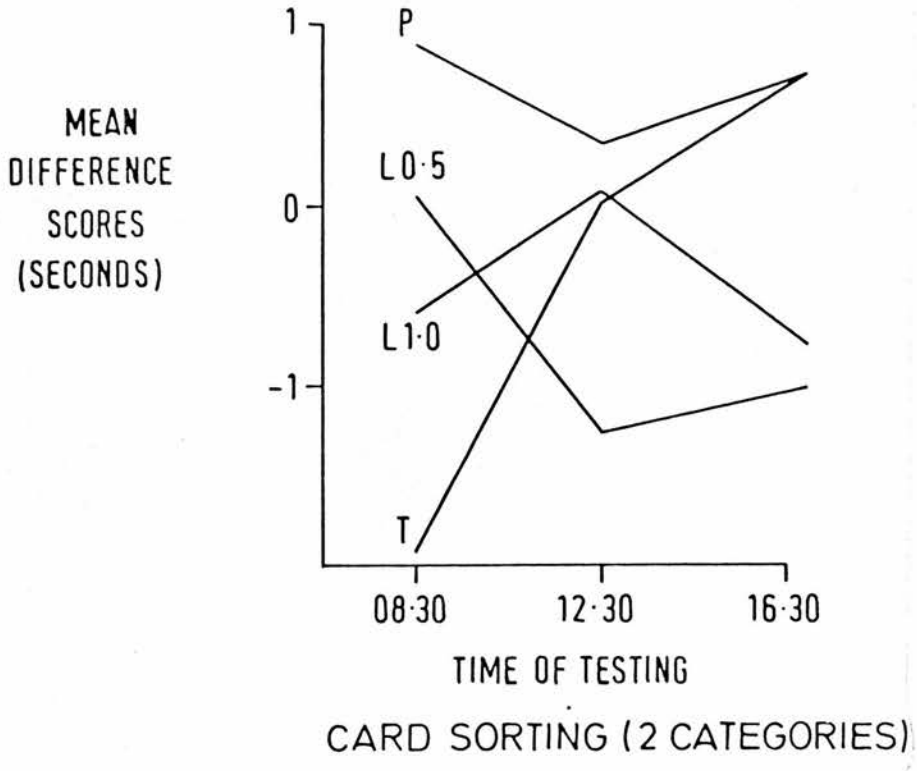


Figure 3:8 Effects of two hypnotics on choice reaction time by time of day

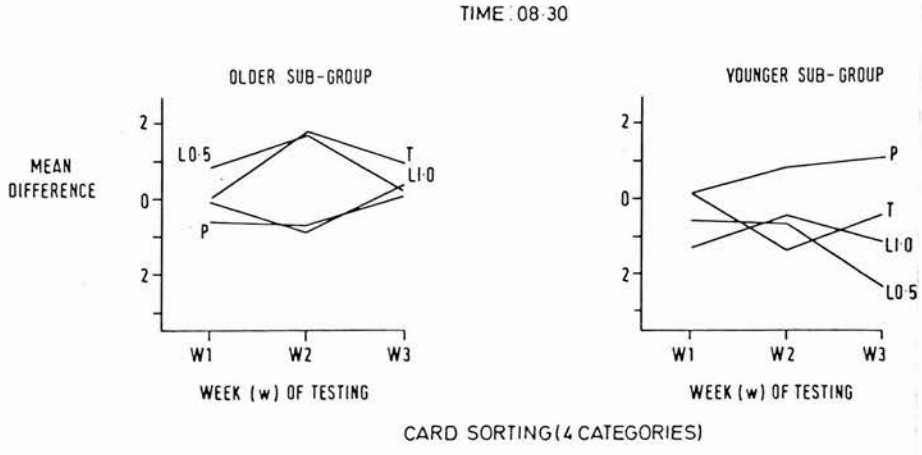


Figure 3:9a Effects of two hypnotics on choice reaction time by age group: 08.30

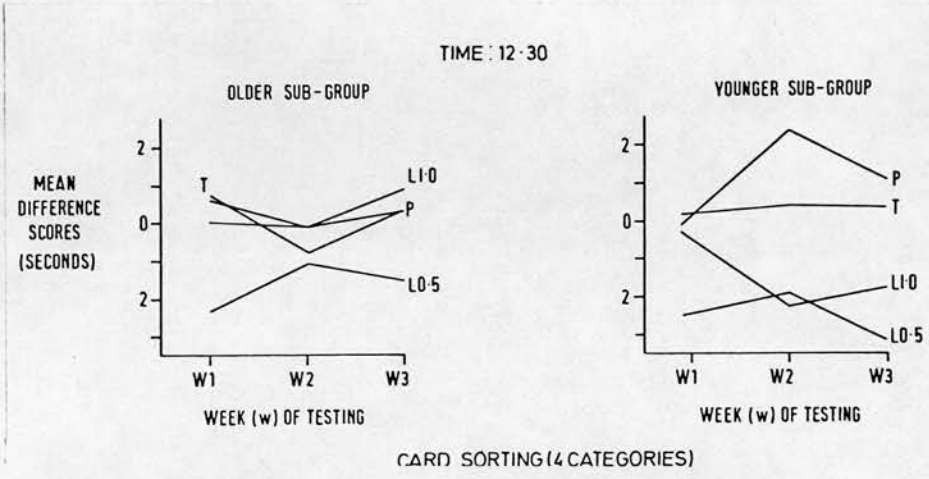


Figure 3:9b Effects of two hypnotics on choice reaction time by age group: 12.30

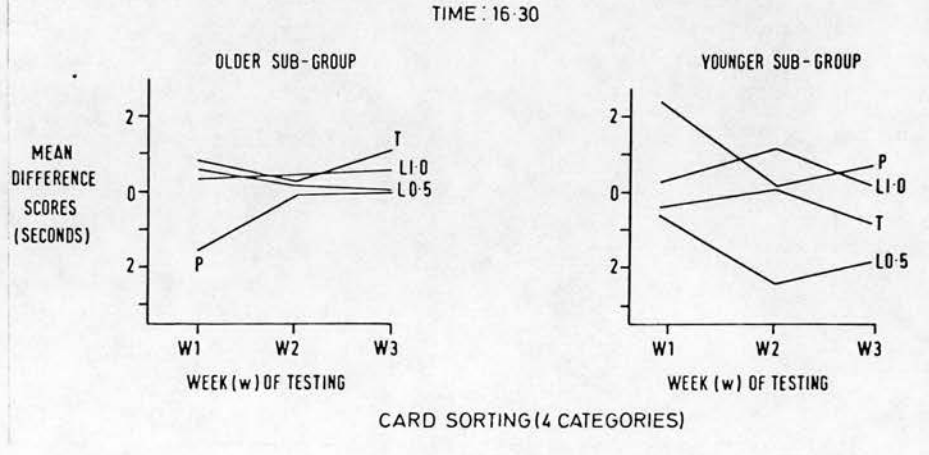


Figure 3:9c Effects of two hypnotics on choice reaction time by age group: 16.30

Table 3:7 Choice reaction time (two category) from the card sorting task: paired comparisons between drug treatment means for each time of testing

Ø8.3Ø Testing Sessions

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L1.Ø (-Ø.59; 1.57)		P (Ø.88; 1.49)	2.24*
T (-Ø.19; 2.68)		P (Ø.88; 1.49)	1.85
LØ.5 (Ø.12; 1.76)		P (Ø.88; 1.49)	1.22
L1.Ø (-Ø.59; 1.57)		T (-1.19; 2.68)	Ø.67
L1.Ø (-Ø.59; 1.57)		LØ.5 (Ø.12; 1.76)	Ø.83
T (-1.19; 2.68)		LØ.5 (Ø.12; 1.76)	1.38

12.3Ø Testing Sessions

L1.Ø (Ø.Ø2; 1.76)		P (Ø.32; 1.34)	Ø.46
T (Ø.Ø1; 2.2Ø)		P (Ø.32; 1.34)	Ø.39
LØ.5 (-1.26; 2.74)		P (Ø.32; 1.34)	1.53
L1.Ø (Ø.Ø2; 1.76)		T (Ø.Ø1; 2.2Ø)	Ø.Ø1
L1.Ø (Ø.Ø2; 1.76)		LØ.5 (-1.26; 2.74)	1.32
T (Ø.Ø1; 2.2Ø)		LØ.5 (-1.26; 2.74)	1.19

16.3Ø Testing Sessions

L1.Ø (-Ø.83; 1.56)		P (Ø.7Ø; 1.9Ø)	1.96
T (Ø.69; 1.44)		P (Ø.7Ø; 1.9Ø)	Ø.Ø1
LØ.5 (-1.Ø3; 2.16)		P (Ø.7Ø; 1.9Ø)	1.72
L1.Ø (-Ø.83; 1.56)		T (Ø.69; 1.44)	2.17*
L1.Ø (-Ø.83; 1.56)		LØ.5 (-1.Ø3; 2.16)	Ø.22
T (Ø.69; 1.44)		LØ.5 (-1.Ø3; 2.16)	2.78**

* $p<Ø.Ø5$
** $p<Ø.Ø1$

Table 3:8 Paired comparisons between treatment conditions for card sorting into four categories (choice reaction time)

	Older sub-group			Younger sub-group			
Drug	P	Ll.Ø	T	P	Ll.Ø	T	Time
			Week 1				
Ll.Ø	Ø.22	-	-	Ø.62	-	-	
T	Ø.47	Ø.11	-	Ø.21	1.Ø4	-	Ø8.3Ø
LØ.5	1.8Ø	Ø.58	Ø.57	Ø.51	Ø.31	Ø.44	
Ll.Ø	Ø.34	-	-	Ø.15	-	-	
T	Ø.6Ø	Ø.1Ø	-	Ø.12	Ø.61	-	12.3Ø
LØ.5	2.Ø2	3.23*	2.12	1.24	1.23	1.13	
Ll.Ø	1.98	-	-	1.78	-	-	
T	1.64	Ø.45	-	1.86	Ø.46	-	16.3Ø
LØ.5	1.49	Ø.Ø9	Ø.19	3.24*	1.53	3.51**	
			Week 2				
Ll.Ø	Ø.Ø4	-	-	Ø.97	-	-	
T	1.85	2.74*	-	1.77	Ø.49	-	Ø8.3Ø
LØ.5	2.18	1.1Ø	Ø.Ø7	1.96	Ø.ØØ	Ø.7Ø	
Ll.Ø	Ø.Ø1	-	-	2.83*	-	-	
T	Ø.33	Ø.68	-	1.59	2.93*	-	12.3Ø
LØ.5	Ø.5Ø	Ø.67	Ø.32	7.36**	Ø.17	1.72	
Ll.Ø	Ø.98	-	-	Ø.42	-	-	
T	Ø.35	Ø.Ø7	-	Ø.Ø1	Ø.6Ø	-	16.3Ø
LØ.5	Ø.31	Ø.14	Ø.22	1.88	1.85	6.67**	
			Week 3				
Ll.Ø	Ø.Ø7	-	-	1.63	-	-	
T	Ø.48	Ø.59	-	1.52	Ø.4Ø	-	Ø8.3Ø
LØ.5	Ø.Ø3	Ø.Ø9	Ø.57	2.Ø5	Ø.5Ø	2.12	
Ll.Ø	Ø.63	-	-	2.58*	-	-	
T	Ø.ØØ	Ø.89	-	Ø.66	1.5Ø	-	12.3Ø
LØ.5	2.18	3.26*	2.76*	3.22*	1.17	2.12	
Ll.Ø	Ø.62	-	-	Ø.26	-	-	
T	1.18	Ø.55	-	2.24	Ø.71	-	16.3Ø
LØ.5	Ø.2Ø	Ø.67	Ø.93	2.58*	Ø.87	Ø.76	

* $p<Ø.Ø5$
** $p<Ø.Ø1$

Values shown are for t (correlated), df = 5, two-tailed probabilities

significant main effect of drug, and no significant interaction effects between drug and age, or between drug and week at these times of testing. However, separate analysis of the 12.30 test session data showed a significant drug main effect ($F = 4.06$, $df = 3,30$, $p<0.05$) which was independent of both the age, and the weeks factors. Within each sub-group, and for each week of testing, paired comparisons between the drug conditions for the 08.30, 12.30, and 16.30 test sessions are shown in Table 3:8. For the 12.30 test sessions, the cell means for each drug condition are compared in Table 3:9.

In the eight-category condition choice reaction time showed no significant main effect of drug, and no significant interaction effects between drug and age, or between drug and either of the test occasions factors.

Manual Dexterity

Analysis of the data from the manual dexterity test showed no significant main effect of drug, but did show a significant interaction effect between drug treatment and time of testing ($F = 2.28$, $df = 6,60$, $p<0.05$), and also showed a significant interaction between the drug, week, time and age factors ($F = 2.13$, $df = 12,120$, $p<0.05$). The drug x time interaction is shown in Figure 3:10, and paired comparisons between the drug means at each time of testing are shown in Table 3:10. The analysis of variance was then repeated for the 08.30, 12.30, and 16.30 times

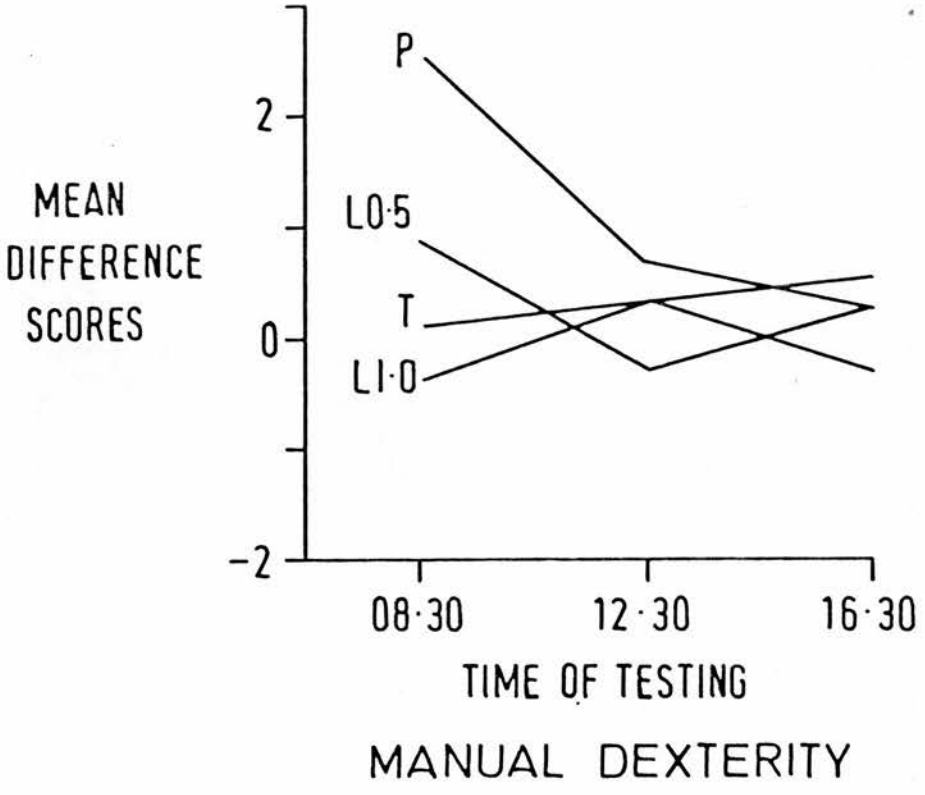


Figure 3:10 Effects of two hypnotics on manual dexterity at each time of testing

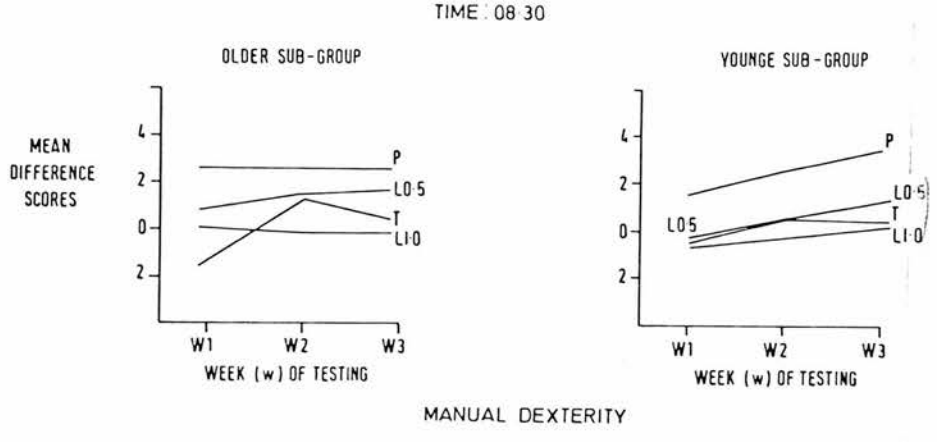


Figure 3:11a Effects of two hypnotics on manual dexterity scores: 08.30

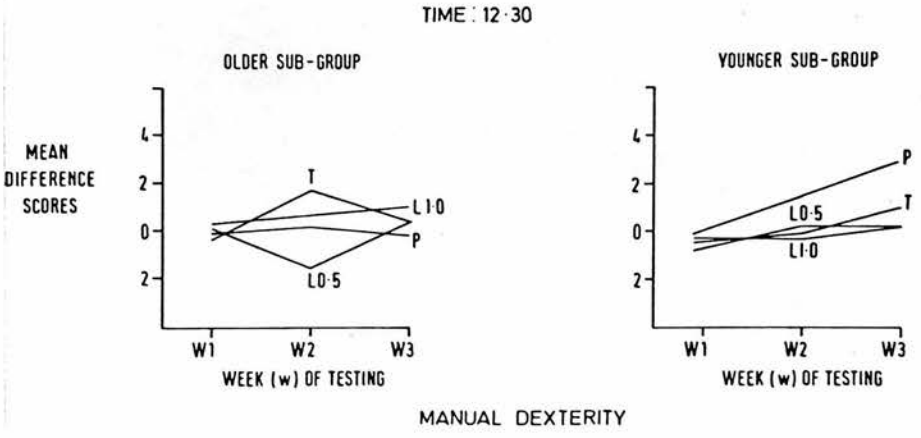


Figure 3:11b Effects of two hypnotics on manual dexterity scores: 12.30

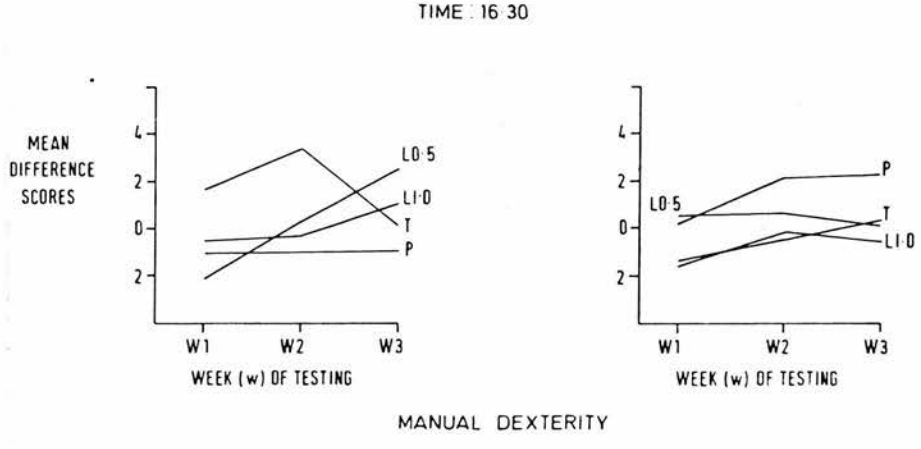


Figure 3:11c Effects of two hypnotics on manual dexterity scores: 16.30

Table 3:9 Card sorting into four categories (choice reaction time): paired comparisons between treatment means for the 12.30 testing

Drug Treatment (Mean; SD)	Placebo (0.57; 1.76)	Loprazolam 1.0	Triazolam 0.5
Loprazolam 1.0 (-0.52; 2.49)	t = 1.06	-	-
Triazolam 0.5 (0.22; 1.98)	t = 0.41	t = 1.22	-
Loprazolam 0.5 (-2.11; 2.19)	t = 3.31**	t = 2.00	t = 2.55*

Values shown are for t (correlated)

Table 3:10 Manual dexterity: paired comparisons between treatment means for each time of testing

08.30 Testing Sessions

Drug Treatment (mean; SD)	v	Drug Treatment (mean ; SD)	t-value
L1.0 (0.31; 2.95)	P	(-2.48; 3.67)	2.41*
T (-0.10; 1.54)	P	(-2.48; 3.67)	2.37*
L0.5 (-0.91; 1.89)	P	(-2.48; 3.67)	1.24
L1.0 (0.31; 2.95)	T	(-0.10; 1.54)	0.40
L1.0 (0.31; 2.95)	L0.5	(0.31; 2.95)	1.50
T (-0.10; 1.54)	L0.5	(0.31; 2.95)	1.17

12.30 Testing Sessions

L1.0 (-0.30; 2.67)	P	(-0.68; 3.06)	0.39
T (-0.34; 1.93)	P	(-0.68; 3.06)	0.30
L0.5 (0.25; 1.41)	P	(-0.68; 3.06)	1.21
L1.0 (-0.30; 2.67)	T	(-0.34; 1.93)	0.04
L1.0 (-0.30; 2.67)	L0.5	(0.25; 1.41)	0.65
T (-0.34; 1.93)	L0.5	(0.25; 1.41)	0.71

16.30 Testing Sessions

L1.0 (0.36; 2.19)	P	(-0.25, 2.45)	0.79
T (-0.51; 2.81)	P	(-0.25; 2.45)	0.27
L0.5 (-0.24; 2.43)	P	(-0.25; 2.45)	0.00
L1.0 (0.36; 2.19)	T	(-0.51; 2.81)	1.06
L1.0 (0.36; 2.19)	L0.5	(-0.24; 2.43)	0.69
T (-0.51; 2.91)	L0.5	(-0.24; 2.43)	0.31

* $p<0.05$ ** $p<0.01$

Table 3:11 Paired comparisons between treatment conditions for manual dexterity scores

	Older sub-group			Younger sub-group			
Drug	P	Ll.Ø	T	P	Ll.Ø	T	Time
			Week 1				
Ll.Ø	1.4Ø	-	-	2.Ø5	-	-	
T	2.17	Ø.97	-	1.93	Ø.32	-	Ø8.3Ø
LØ.5	1.13	Ø.72	2.63*	1.44	Ø.51	Ø.Ø5	
Ll.Ø	Ø.36	-	-	Ø.Ø8	-	-	
T	Ø.35	Ø.47	-	Ø.15	Ø.12	-	12.3Ø
LØ.5	Ø.34	Ø.11	Ø.46	Ø.67	1.21	1.Ø2	
Ll.Ø	Ø.8Ø	-	-	2.11	-	-	
T	3.Ø6*	3.Ø6*	-	5.19**	Ø.Ø2	-	16.3Ø
LØ.5	Ø.43	Ø.51	1.24	Ø.66	3.Ø6*	4.12**	
			Week 2				
Ll.Ø	1.4Ø	-	-	1.6Ø	-	-	
T	Ø.61	1.29	-	Ø.83	Ø.55	-	Ø8.3Ø
LØ.5	Ø.34	1.24	Ø.Ø6	Ø.93	2.3Ø	Ø.ØØ	
Ll.Ø	Ø.3Ø	-	-	Ø.87	-	-	
T	Ø.93	Ø.45	-	Ø.61	Ø.Ø3	-	12.3Ø
LØ.5	1.28	1.28	1.79	Ø.82	Ø.31	Ø.17	
Ll.Ø	Ø.56	-	-	1.51	-	-	
T	4.77**	2.43*	-	1.57	Ø.41	-	16.3Ø
LØ.5	1.24	Ø.4Ø	2.Ø2	Ø.89	Ø.89	1.34	
			Week 3				
Ll.Ø	1.Ø3	-	-	1.89	-	-	
T	Ø.68	Ø.26	-	2.77*	Ø.11	-	Ø8.3Ø
LØ.5	Ø.18	Ø.71	2.Ø4	1.87	Ø.86	Ø.74	
Ll.Ø	1.Ø5	-	-	1.61	-	-	
T	Ø.83	Ø.33	-	1.19	Ø.28	-	12.3Ø
LØ.5	Ø.73	Ø.38	Ø.Ø7	2.Ø4	Ø.Ø3	Ø.18	
Ll.Ø	1.93	-	-	1.Ø3	-	-	
T	Ø.97	Ø.5Ø	-	Ø.88	Ø.32	-	16.3Ø
LØ.5	2.44*	1.ØØ	1.33	1.36	Ø.26	Ø.23	

* p<Ø.Ø5 ** p<Ø.Ø1

Values are shown for t (correlated), df = 5, two-tailed probabilities

Table 3:12 Withdrawal Week: summary of results from main analyses of variance (F values)

Test/Variable	Main Effects	Interaction Effects		
	Drug	D x A	D x T	D x T x A
Auditory Vigilance:				
% detections (1 hour)	0.93	0.37	0.16	0.47
% detections (final 40 min)	0.14	0.29	0.09	1.02
false reports	0.13	2.04	0.90	0.88
Digit Symbol Substitution	1.39	1.16	0.70	0.39
Card Sorting:				
movement time (2 category)	1.30	1.32	0.78	0.56
movement time (4 category)	2.20	0.55	0.79	0.78
movement time (8 category)	0.80	0.88	1.66	0.18
Choice Reaction Time				
(2 category)	1.89	0.41	1.04	0.96
(4 category)	1.70	1.27	0.99	0.95
(8 category)	0.67	0.27	1.21	1.47
Manual Dexterity	0.26	0.42	1.21	0.74

D = Drug (treatment)
A = Age (grouping)
T = Time (of day)

of testing. The results of these further analyses are shown in Figures 3:11a, 3:11b, and 3:11c respectively. At the 08.30 and 12.30 times of testing, separate analyses of variance showed no main effects of drug, and no significant interaction effects between drug and age, or between drug and week. At the 16.30 time of testing, however, a significant interaction was found between drug and age ($F = 3.37$, $df = 3,30$, $p<0.05$). Within each sub-group, and for each week of testing, paired comparisons between the drug conditions for the 08.30, 12.30 and 16.30 test sessions are shown in Table 3:11.

Withdrawal Data

The effects of withdrawal on performance for each of the treatment conditions are summarized in Table 3:12. None of the test measurements analyzed showed a significant main effect of drug condition, and none showed significant interactions between drug and age, or between drug and time of testing.

Discussion

Results will be discussed in the order presented in the previous section. A summary of conclusions is presented at the end of this chapter.

Auditory Vigilance (correct detections)

Efficiency on vigilance tasks declines progressively as time-on-task increases (Mackworth, 1969). Several researchers have reported that both sedative and stimulant drug influences on vigilance performance are greatest during the latter portions of the task, when vigilance is normally lowest (e.g. Loeb et al. 1965). Hart et al.(1976), assessing the acute influence of amylobarbitone and diazepam on performance in a one-hour auditory vigilance task, analyzed correct detections for each successive quarter-hour period. These researchers found that the progressive decrement, typical of sustained vigilance performance, was greatest between the first and second quarter-hour periods irrespective of drug treatment. Thus, for a one hour auditory vigilance task, it is likely that the latter three quarter-hour periods are more sensitive to residual drug influences. As the data from the present task were collected in 10min units, the latter 40min of the task were analyzed in addition to the data collected for the full one hour.

The differential sensitivity to residual drug effects of early and late portions of the auditory vigilance task is reflected in Table 3:1. While correct detections for the full one hour show no significant main or interaction effects, correct detections for the final 40min of the task show a significant influence of drug which interacts with age, time and week. Table 3:2 shows that, across all times and weeks of testing, and across both sub-groups, only one drug treatment, loprazolam 0.5mg, differed significantly from placebo. Triazolam 0.5mg and loprazolam 1.0mg show no significant departure from placebo

levels of performance. However, performance associated with loprazolam Ø.5mg was significantly inferior to that which obtained under the placebo condition.

This main drug effect was not independent of the age, week, or time factors. Figures 3:2a, 3:2b, and 3:2c show that loprazolam Ø.5mg was consistently associated with the lowest levels of performance in the older sub-group for all times of testing. This is particularly the case for the 12.3Ø sessions (Figure 3:2b), where loprazolam Ø.5mg is associated with the lowest percentage of correct detections for all three weekly testing sessions. For the younger sub-group, performance during the loprazolam Ø.5mg condition is, nevertheless, low when compared with the loprazolam 1.Ømg, and the triazolam condition. An interesting feature of Figures 3:2a, 3:2b and 3:2c is the tendency shown, particularly in the younger sub-group, for test scores to improve over the three weekly testing sessions. Pre drug-treatment practice sessions, and a further baseline week (see Figure 2:1), should have minimized the impact of practice on the drug treatment data. Nevertheless, week 3 scores among the younger sub-group for the active drug conditions are generally higher than week 1 scores, the only exception to this being the loprazolam Ø.5mg values at 16.3Ø (Figure 3:2c). These data, then, do not suggest cumulative drug effects arising from repeated ingestion of the experimental treatments.

Whether this improvement in performance over weeks represents a genuine practice effect, or whether it reflects the ability of

subjects to compensate for the residual effects of drugs is not entirely clear. However, considering only the Ø8.3Ø testing sessions (Figure 3:2a) the latter conclusion, that of compensating for residual drug effects, gains credibility. Re-analysis of the Ø8.3Ø testing session data showed a further significant drug x week x age interaction. If practice effects per se were responsible for the improvements shown over weeks, then placebo scores ought equally to be affected. This is clearly not the case for the younger sub-group. While placebo scores are associated with the highest level of performance relative to the baseline mean, this condition shows similar levels of performance maintained over the three weekly testing sessions. Scores for the three active drug treatments, however, begin at low levels, and only exceed baseline mean values in week 3. If we reasonably assume that residual drug effects will be maximal in the early morning, then, for the younger sub-group, this pattern of performance is consistent with compensation for drug effects over time. Within the older sub-group, such improvements are less evident, and placebo values more labile. Individual comparisons between drug conditions within each sub-group, and for each week and time of testing, yielded few significant differenes (Table 3:3). Comparisons which did produce significant t-values occurred with a frequency no greater than that to be expected by chance alone (with alpha at the 5% level). Such results caution against over interpretation.

In general, then, the effects of loprazolam 1.Ømg and Ø.5mg, and triazolam Ø.5mg on correct detections present an apparently

paradoxical result. While the higher dose of loprazolam, and triazolam Ø.5mg appear not to impair performance, the lower dose of loprazolam produces significant performance decrements relative both to placebo ($p<Ø.Ø5$) and to triazolam ($p<Ø.Ø5$; Table 3:2). Such a result, however, is not entirely inconsistent with previous research concerning either vigilance performance alone, or drug effects on vigilance performance. Hart et al. (1976) tested subjects for one hour on the Wilkinson auditory vigilance task 45min after the administration of diazepam 2.5mg and 5mg, and amylobarbitone 5Ømg and 1ØØmg, and placebo. While both doses of diazepam, and the lower dose of amylobarbitone significantly impaired performance (as measured by the number of correct detections), the higher dose of amylobarbitone did not. Furthermore, the decrement produced by the diazepam condition was greatest for the lower (2.5mg) dose.

With regard to the present data, at least two hypotheses may be advanced to account for the pattern of drug effects on auditory vigilance performance. Firstly, given that all the subjects considered themselves to be poor sleepers, improved sleep quality following loprazolam 1.Ømg and triazolam Ø.5mg, but not following loprazolam Ø.5mg, may have differentially affected subsequent vigilance performance. If, for example, subjects were ordinarily below optimal vigilance levels due to poor sleep, then an effective hypnotic, or an effective dose of an hypnotic, by improving sleep quality, may enhance performance on the auditory vigilance task. It is evident from Table 3:2, however, that the

highest mean level of performance is associated with placebo, and from Figures 3:2a, 3:2b, and 3:2c, that performance levels for the three hypnotics, more often than not, fail to exceed original baseline values. Such a pattern is inconsistent with improved performance under the active drug treatments.

A second hypothesis concerns the motivation of subjects. Mackworth (1970) has reviewed a series of studies concerning auditory vigilance performance in which the motivation of subjects, and subsequent performance on the vigilance task, has been improved. Thus, vigilance performance can improve if the subject's motivation (or effort) is increased through, for example, the use of rewards, providing knowledge of results, etc. In the present context, the subject's own perception of atypical drowsiness or reduced attention may have 'cued' changes in his or her motivational state, increasing the effort to remain alert, and thus compensating for the deleterious effects of sedation. This hypothesis would predict that, if feelings of drowsiness were greatest for loprazolam 1.0mg and triazolam 0.5mg, and least for loprazolam 0.5mg, then any adjustments in motivation would follow a similar pattern, being least for loprazolam 0.5mg. Support for this hypothesis is provided by the daily subjective ratings of morning vigilance completed by each subject throughout the study, and fully described in the next chapter. Suffice it to point out here that, irrespective of age sub-group, subjects consistently rated themselves as less vigilant during the loprazolam 1.0mg and triazolam conditions than during the loprazolam 0.5mg condition ($p<0.05$ for both comparisons; Table 4:4a). Indeed, mean

subjective ratings of vigilance during the three weeks of loprazolam Ø.5mg consumption deviated little from placebo values.

Similar motivational influences have been reported in the literature concerning alcohol and performance. Williams et al. (1978) used a balanced placebo design to assess the effects of zero, Ø.Ø3, and Ø.Ø6 percent blood alcohol levels on cognitive and motor tasks which included a letter cancellation test, the WAIS digit span, and Raven's Progressive Matrices. According to this design, half the subjects receiving alcohol are told they are receiving placebo, while half the subjects receiving placebo are told they are receiving alcohol. The remaining halves are correctly informed as to the nature of the experimental treatment. The results showed that, among those expecting and receiving alcohol, performance improved as the dose of alcohol increased.

When the subjective experience of an individual can reliably distinguish between one drug condition and another, (as appears to be the case in the present study), then the advantages of a double-blind procedure are greatly reduced, and the data may become systematically influenced by motivational changes in the individuals concerned. It is also probable that such compensatory strategies are learned progressively, and are subject to improvement over time. With reference to the Ø8.3Ø testing sessions (Figure 3:2a), the relative stability of the placebo scores for the younger sub-group, and the overall improvement between weeks 1 and 3 shown for the active drug conditions accord with this view, and further suggest that such strategies were

better learned by the younger, than by the older sub-group.

Auditory Vigilance (False Positive Reports)

False positive responses occurred with a low frequency throughout the experiment, with scores of zero, or one per hour not infrequently recorded. Binford and Loeb (1966), analyzing the effects of repeated sessions on auditory vigilance performance, found that false positives began at high levels in the early sessions, and rapidly declined in later sessions as the subject apparently learns about the distribution of signals, and also learns to distinguish more efficiently between signal and noise. A similar trend was apparent in the present data. False positive reports were highest during the practice and baseline weeks, and lowest during the subsequent drug and withdrawal weeks. To maintain comparability with previous studies, the mean absolute number of false positive reports were analysed.

While the number of false positive reports showed no significant main effect of drug (Table 3:1), the age factor did emerge as a significant main effect ($F = 5.11$; $df = 1,10$; $p<0.05$; for analysis of variance table see Appendix 2:3). With the single exception of placebo scores at 12.30 (Figure 3:3), the younger sub-group invariably made fewer false positve reports for each drug condition at each time of testing. It is also apparent from Figure 3:3 that the relative position of the drug condition values for the older sub-group remained fairly constant for each time of testing, though again, with the 12.30 testing sessions being the

only exception. Thus, for the older sub group, the highest frequency of false positive reporting was associated with triazolam, followed by loprazolam 1.Ømg, and placebo. For both sub-groups, however, loprazolam Ø.5mg was associated with the lowest levels of false positive reporting.

Interestingly, while triazolam Ø.5mg was associated with the highest levels of false positive reporting in the older sub-group, the converse applied to the younger sub-group, particularly at the Ø8.3Ø and 16.3Ø testing sessions (Figure 3:3). This difference in the response of the two sub-groups to the same drug condition is better illustrated in Figures 3:4a, 3:4b, and 3:4c. For the older sub-group, triazolam is consistently associated with high levels of false positive reporting in week 3 for all times of testing. On the other hand, triazolam values for the younger sub-group are both lower, and show more stability, over the three weeks of testing.

False positive reports reflect, to some extent, the degree of caution exercised by the subject. When caution is high, false reports are correspondingly low; as caution decreases, false positive reports increase. Typically, sedative drugs are reported to increase the frequency of false positive reports on vigilance tasks (Loeb et al. 1965; Neal and Pearson, 1966). Hart et al. (1976) also found that amylobarbitone 1ØØmg was associated with an increase in false positive reports on auditory vigilance, an effect which wore off after 4h. In the present study, none of the active drug conditions significantly influenced the degree of

caution shown by the younger sub-group. In the older sub-group, however, differences between the triazolam and loprazolam Ø.5mg conditions (see Table 3:4) suggest a selective effect of the active drugs. Specifically, among the older sub-group, triazolam is associated with a progressive lowering of caution, relative to loprazolam Ø.5mg, between the first and the third testing weeks. Considered in relation to the correct detections data, this reduction in caution among the older subjects during the triazolam condition is not associated with any increase in the efficiency of target detections. The low levels of false positive reports for the loprazolam Ø.5mg condition, however, is associated with a similarly low level of correct detections (particularly among the older sub-group), suggesting a rather generalized suppression of responding during this drug condition.

Card Sorting (movement times)

Both the two-, and eight-category movement times from the card sorting task showed significant drug influences on performance. For the two-category condition, the drug factor interacted with the week and time factors, and for the eight-category condition the drug factor interacted independently with age, and with time (see Table 3:1). The movement time component of the card sorting task has been interpreted as a measure of motor speed and coordination (e.g. Malpas and Joyce, 1969). Results from the two- and eight-category conditions will be considered together.

For the two-category condition Figure 3:5 shows few distinct differences between the drug treatments. Relative to placebo, movement times were significantly slower following loprazolam 1.Ømg at the Ø8.3Ø testing session on week 1 (Table 3:5). Table 3:5 also shows that, for the 16.3Ø testing sessions, sorting times following loprazolam Ø.5mg were significantly faster than placebo in week 1, and significantly faster than loprazolam 1.Ømg in week 2. Again, considering the number of paired comparisons made, the occurrence of significant t-values with a frequency no greater than would be expected by chance alone cautions against over-interpretation. Re-analysis of each time of testing separately revealed no further significant main effects of, nor interaction effects with the drug factor. It is interesting to note, however, that both the Ø8.3Ø and 16.3Ø testing sessions showed significant main effects of week, indicating strong practice effects (see Appendix 2:5). The 12.3Ø testing sessions showed no significant improvement over the three weekly test sessions.

For the eight-category sorting times, Figure 3:6 clearly indicates the tendency (also seen in the manual dexterity test) for the younger subjects to show greater improvements with practice under placebo conditions. Indeed, the placebo treatment mean for the older sub-group does not exceed the original baseline mean movement time. While it might appear from the figure that both loprazolam and triazolam improved performance in the older sub-group, paired comparisons between these mean values (Table 3:6a) showed no significant differences. Conversely, Table 3:6a shows that, for the younger sub-group, triazolam Ø.5mg

was associated with significantly impaired performance relative to placebo.

The significant interaction between drug condition and time of testing for the eight-category movement times is shown in Figure 3:7. It can be seen from the figure that the interaction arises from the consistent decline in the speed of performance between Ø8.3Ø and 16.3Ø shown for the placebo and loprazolam 1.Ømg conditions. It is not possible to conclude from these results that any of the drug conditions exerted a systematic influence on performance throughout the day. Paired comparisons between the treatment means for each of these times of testing (Table 3:6) show that for the Ø8.3Ø testing sessions, movement times for the loprazolam Ø.5mg condition were significantly slower than those for placebo, or triazolam. At the 16.3Ø times of testing, performance associated withg loprazolam Ø.5mg was significantly faster that for loprazolam 1.Ømg. These few, and rather erratic, significant differences might plausibly be attributed to random fluctuations in performance throughout the day.

Card Sorting (choice reaction time): two-category

By deducting movement time from the actual time taken to sort the playing cards into their appropriate categories, a measure of central processing time is derived (Crossman, 1953). This measurement, the choice reaction time, represents only the time taken to process the information on 32 cards (i.e. to

recognize the value, and decide upon the destination of 32 cards). Thus, choice reaction time is independent of motor speed, and relatively immune from somatic drug influences (e.g. drug-induced reductions in muscle tone, etc.).

The significant drug x time of testing interaction for the two-category choice reaction time is shown in Figure 3:8. Placebo mean values show a clear superiority over the active drug conditions, with a peak in speed at Ø8.3Ø, an increase in reaction time at 12.3Ø, and some recovery of speed shown at 16.3Ø. Such a pattern is consistent with the circadian variations in performance reported by Kleitman (1963) and Colquhoun (1971), the 12.3Ø results (see Figure 3:8) corresponding to the so called "post-lunch dip" (Colquhoun, 1971).

Table 3:7 shows that at the Ø8.3Ø times of testing, the mean choice reaction time following loprazolam 1.Ømg was signigicantly slower than under placebo conditions. However, while Figure 3:8 suggests particularly poor performance under the triazolam condition at Ø8.3Ø, this effect is more apparent than real. Triazolam scores did not differ from placebo at this time, a finding that can be accounted for by wide scatter in the triazolam data at this time. None of the paired comparisons showed significant differences at 12.3Ø, but triazolam reaction times were significantly faster than both loprazolam Ø.5mg and 1.Ømg at 16.3Ø.

Given that the mean placebo condition reaction times show

typical time of day variations, the drug x time interaction found in this task is not particularly surprising. If performance is impaired by residual drug effects in the early morning (in this case, by loprazolam 1.0mg) some recovery in performance efficiency would be expected as drug effects subside later in the day. That reaction times following loprazolam recovered to placebo levels by the 12.30 testing sessions suggests that, in this case, the residual effects of a relatively short-life hypnotic did not exacerbate normally-occurring troughs in early afternoon performance.

Choice reaction time (four-category)

The significant drug x week x time x age interaction for the four-category choice reaction times (Figures 3:9a, 3:9b, and 3:9c) again illustrates differences in performance efficiency between the two sub-groups. These differences show features similar to the 4-way interaction from the auditory vigilance task. In particular, under placebo conditions, the younger sub-group show a tendency to improve over baseline levels of performance, while the mean performance scores for the older sub-group rarely exceed the baseline mean. None of the drug treatment versus placebo treatment comparisons showed significant differences at the 08.30 times of testing (Table 3:8). At the 12.30 testing sessions, choice reacton times for the younger sub-group under the loprazolam 0.5mg and 1.0mg conditions are significantly slower than under the placebo condition for both week 1 and week 2, while for the 16.30 testing sessions, loprazolam 0.5mg scores differed

significantly from placebo values in weeks 1 and 3. Within the older sub-group, none of the active drug treatment versus placebo comparisons yielded significant t-values (Table 3:8).

In general, then, loprazolam in both 1.0mg and 0.5mg doses was associated with some degree of performance impairment, particularly at the 12.30 times of testing, and particularly among the younger subjects. The analyses of variance for each separate time of testing, however, do not support a view that loprazolam 1.0mg consistently impaired performance, or that loprazolam 0.5mg differentially affected the two sub-groups. The main effect of drug found for the 12.30 testing session was independent of both week and age (Appendix 2:9). Table 3:9 shows that this main effect is principally due to the loprazolam 0.5mg condition; none of the other active drug conditions differed significantly from placebo.

The pattern of impaired performance on choice reaction time is reminiscent of the results obtained from final 40min of the auditory vigilance task. It is particularly relevant to note that, with regards the present test, the significantly lower levels of performance associated with loprazolam 0.5mg are not entirely confined to the 12.30 testing sessions, and can be found, within the younger sub-group, at the 16.30 sessions (Figure 3:9c). Furthermore, among the younger subjects, the 0.5mg dose of loprazolam was consistently associated with the lowest levels of performance at all three times of testing, while among the older subjects, this dose of loprazolam was associated with the lowest

levels of performance for all three weeks at the 12.30 testing sessions. It is unlikely, therefore, that these results reflect random variations in performance leading to spuriously significant differences. This being the case, it is not unreasonable to suggest that the effects of loprazolam 0.5mg on choice reaction time, at a given level of task complexity, are mediated by processes similar to those already proposed in relation to the results from the auditory vigilance task (final 40min). That, in the present case, this effect is more pronounced in the early afternoon, a time associated with a decline in performance efficiency, is suggestive of an interaction between residual drug effects, and circadian variations in performance.

Manual Dexterity

No significant main effect of drug was found in the principal analysis of variance of the manual dexterity data (Table 3:1). Again, however, interaction effects clearly indicate differences between the four drug conditions, such differences depending upon age, and the time and week of testing. For the placebo scores, manual dexterity shows a marked time of day effect (Figure 3:10), with performance declining sharply after the peak levels shown at 08.30 (drug x time interaction: $p<0.05$; Table 3:1). This early morning peak appears to be modified by the active drug treatments, resulting in fairly uniform levels of performance for each time of day. For the 08.30 testing sessions, paired comparisons

between the drug treatment means (Table 3:5) show that loprazolam 1.0mg, and triazolam 0.5mg are associated with significantly impaired performance relative to placebo ($p<0.05$ in both cases). Thus, unlike the performance decrements seen for the more complex vigilance task, simple motor coordination shows a more conventional pattern of drug effects, the larger dose of loprazolam, and triazolam 0.5mg impair performance, but only during the early morning testing sessions.

The results from these paired comparisons should, however, be interpreted with some caution. In the re-analysis of the 08.30 testing sessions using repeated measures analysis of variance (Figure 3.11a), the drug main effect failed to reach the criterion level of significance ($F = 2.73$; $df = 3,30$; $p = 0.061$). For this time of testing, paired comparisons between treatment means within the two sub-groups (Table 3:5b) show only sporadic treatment versus treatment differences (older sub-group week 1: T v L0.5, $p<0.05$; younger sub-group week 3: P v T, $p<0.05$).

For the 12.30 and 16.30 times of testing (Figures 3:11b and 3:11c) the apparent superiority of the placebo scores is maintained only for the younger sub-group. Scores for the older sub-group again show much greater variability. In general, performance on this task was characterized by a marked tendency to improve between week 1 and week 3, evidenced in the main analysis of variance by a significant main effect of week ($F = 9.50$; $df = 2,20$; $p<0.001$; see Appendix 2:11). The pattern of performance shown in Figures 3:11a, 3:11b, and 3:11c also suggests that the younger sub-group, under placebo conditions, showed a greater tendency to improve

over time. Once again, however, it is not possible to interpret these improvements as simple practice effects under each drug condition.

At all times of testing, particularly for the younger sub-group, improvement over weeks for placebo values might reasonably be interpreted as a practice effect per se, with week 1 scores being equivalent to, or exceeding, the original baseline mean. This interpretation is not appropriate in the case of the active drug condition scores. Active drug scores for week 1, especially those for loprazolam 1.0mg and triazolam 0.5mg, are generally below baseline, exceeding this value only in week 3. Thus, as was the case for correct detections (final 40min) on the auditory vigilance task, the pattern of results for the active drug conditions shown in Figures 3:11a, 3:11b, and 3:11c is not entirely consistent with a true practice effect, but rather, may reflect a complex interaction between drug condition and practice effects. That such an interaction appears to be more pronounced in the younger subjects may be attributable to the greater variability in performance shown by the older sub-group.

In conclusion, loprazolam 1.0mg and triazolam 0.5mg were associated with performance decrements relative to placebo on the manual dexterity test. This decrement was confined to the early morning (08.30) testing sessions. There is no evidence of a cumulative drug effect on performance.

Summary of Results and Conclusions

In a multiple dose trial which allowed reasonable time for the development of culmulative effects, short-life hypnotics of the type used in the present experiment were not associated with the profound performance decrements reported for longer acting hypnotics like nitrazepam (e.g. Bond and Lader, 1972) or flurazepam (e.g. Oswald et al. 1979). Nevertheless, the present results do indicate that both triazolam and loprazolam, in clinically recommended doses, can impair performance on a variety of tasks. Overall, such impairment as there was did not emerge as a general and easily recognized reduction in performance efficiency, but emerged, rather, as a subtle and often complex interaction with age, time of day, and week of testing. Drug influences also appeared to be selective with regard to both the dose used, and the tasks affected. Impairment clearly associated with loprazolam 1.0mg and triazolam 0.5mg was confined to the manual dexterity task (08.30 testing sessions), and the card-sorting movement times (two- and eight-category). Both tasks are primarily measures of motor speed, and perceptual motor coordination. In contrast, impairment associated with loprazolam 0.5mg is evident in those tasks requiring attention and information processing skills (viz. auditory vigilance and choice reaction time [four-category]).

Considered in functional terms, the higher dose of loprazolam, and triazolam 0.5mg were detrimental to performance

only on those tasks which showed a significant degree of improvement over the three week experimental period. On the other hand, neither the auditory vigilance task, nor the choice reaction time task, showed a significant main effect of week in the main analyses of variance. Thus, the performance decrements seen on some of the motor tasks in the present experiment may have occurred, not because of a deterioration in the level of performance as such, but rather because the tendency to improve with practice, or the effects of earlier pre-drug practice sessions, was attenuated. The performance curves shown in Figure 3:11a for the manual dexterity task certainly accord with this view.

Differences between the drug treatments, especially differences between loprazolam 1.0mg and triazolam 0.5mg (both relatively high doses), are not particularly distinct in the present study. One such effect, the progressive increase in false positive reports associated with triazolam on the auditory vigilance task for the older sub-group, will be discussed in the next chapter.

The results will now be summarized in relation to the three non-drug factors of particular interest in this experiment, i.e. the duration of drug usage, the time of performance testing, and the age of the subjects.

Duration of drug usage

Overall, the effects on performance of loprazolam Ø.5mg and 1.Ømg, and triazolam Ø.5mg reported here are not consistent with drug accumulation over the 16 day treatment periods. None of the performance measures showed a progressive decrement over time, and, in some cases, performance is actually shown to improve under the active drug conditions, though at an apparently slower rate than performance associated with placebo.

Time of day

None of the experimental treatments was associated with sustained performance decrements throughout the day. With regards the larger dose of loprazolam, and triazolam Ø.5mg, the early morning testing sessions appeared to be most sensitive to drug effects. In this respect, the present results accord with those previous acute studies which report an absence of drug impairment 1Øh after the ingestion of loprazolam Ø.5mg, 1.Ømg, and 2.Ømg (Hindmarch and Clyde, 198Ø), and 16h after triazolam Ø.5mg or 1.Ømg (Veldkamp et al. 1974).

Three of the performance measures showed significant drug x time interactions: card sorting movement times (eight-category); choice reaction time (two-category); and manual dexterity. For all three tasks, the performance curves (Figures 3:7, 3:8, and 3:1Ø respectively) show a peak in efficiency at the Ø8.3Ø testing sessions, and a decline in performance efficiency at 12.3Ø. Considered in relation to "post-lunch" effects, it should be remembered that the 12.3Ø testing sessions commenced at 12.3Ø;

all the above three tasks followed the one hour auditory vigilance task, and were conducted, therefore, between 13.30 and 14.30. None of these interactions provides convincing evidence that any of the experimental treatments significantly exacerbated normally occurring "dips" in diurnal performance efficiency. Results from the four-category choice reaction time task, however, clearly show selective impairment for the loprazolam 0.5mg condition at the 12.30 testing session (Figure 3:9b). While, in context, this single result appears to be an isolated finding, it nevertheless does not allow the conclusion that the active drugs did not interact with circadian variations in performance efficiency.

Age of subjects

The pervasive influence of age on the present results clearly justifies the attention paid to this factor. Of the ten significant interactions shown in Table 3:1, six include the age factor. In general, the older subjects did not show a greater sensitivity to the drug treatments. Any such differential response to the active drugs, however, may have been masked by the broad, and consistent, inter-group differences in the overall pattern of performance. Under placebo conditions, mean scores for the older sub-group tended to be lower, more labile, and less likely to improve with practice, than those of the younger sub-group. Indeed, these characteristics in the performance of the older sub-group suggest that, in many cases, these subjects were not performing at peak levels throughout the experiment, particularly in those tasks which loaded heavily on motor skills.

If this was the case, then such performance would be less likely to show drug-induced decrements than would be the performance of subjects working closer to the 'ceiling' of their abilities. This would certainly explain why, on some of the tasks, (see, for example, Figure 3:9a) performance in the younger sub-group appears to be more consistently affected by the active drug treatments. Nevertheless, in some of the tasks showing impairment for both sub-groups (e.g. correct detections on auditory vigilance) there is a clear tendency for the effect to be more profound in the older subjects.

Differences between the sub-groups <u>are</u> present in the false-alarm data from the auditory vigilance task. While triazolam decreased caution in the older subjects, this drug was associated with an increase in caution among the younger subjects. This result also represents one of the few differences observed between the effects of loprazolam, and the effects of triazolam on performance. In the older sub-group, false alarms associated with loprazolam tended to decrease. As this difference between the two drug conditions is also reflected in the daily subjective ratings of anxiety, the drug and age differences present in the false alarm data will be discussed in the next chapter. Suffice it to point out now that the false alarm data does admit the possibility of differential responses to short-life hypnotic drugs between the early and late middle-aged.

Any attempt to identify, or to interpret, the effects on performance of sedative-hypnotic drugs must take into account variables affecting the drug-performance relationship. On theoretical grounds, drugs which improve the sleep quality of otherwise poor sleepers, but which are nevertheless devoid of residual activity, may be expected actually to improve performance by reducing sleepiness and fatigue. Motivational changes arising from, for example, improved sleep quality, reduced daytime fatigue, or reductions in daytime anxiety following the use of sedative-hypnotic drugs, may all contribute to the resulting pattern of measured performance. It is clear from previous experiments, however, that the detrimental sedative effects of potent long-acting hypnotics may supersede many of these possible advantages, producing a generalized, and consistent, reduction in performance efficiency which affects motor and cognitive tasks alike (e.g. the results reported by Oswald et al. [1979] for flurazepam). Results from the present experiment demonstrate that this is not the case for either loprazolam or triazolam. Behavioural advantages arising from the use of hypnotic drugs compete with the behavioural disadvantages. Where these disadvantages are clearly dominant (as with high-dose flurazepam), the effects on performance appear relatively straightforward. Where, however, residual daytime sedation is not a dominant characteristic of a particular drug, then it is reasonable to suppose that any disadvantage arising from its use, (reductions in vigilance for example), is more likely to be modified by appropriate changes in the individuals general 'motivation', leading in turn to a more complex pattern of effects

on performance (as seen in the present study). This ability to compensate for drug effects which appears to mediate several of the results reported here does, however, represents a major advantage in the use of shorter acting, non-cumulative hypnotic drugs.

Chapter 4

Experiment 1: Effects of triazolam and loprazolam on daily ratings of mood and subjective feelings.

Throughout each of the experimental periods described in Chapter 2 (see Figure 2:1) subjects completed daily subjective ratings of sleep quality, morning vigilance, concentration, and anxiety using 10cm line visual analogue scales. These rating forms are reproduced in Appendix 3. Two scales were completed in the morning (Sleep Quality and Morning Vigilance) and two in the evening (Concentration and Anxiety). Subjects were required to make a mark on a 10cm line separating semantically opposed statements. A mark in the centre of the line would indicate no subjectively assessed change from normal. Daily ratings commenced on the morning following the first capsules, and continued until the morning following the last capsules for that period. Thus, for each of the four subjectively rated variables, seven ratings were completed during the placebo (baseline) week, 21 (3 x 7) were completed during the drug/placebo treatment weeks, and seven were completed during the withdrawal week by each subject.

Analysis of data

Rating forms were scored according to a method fully described by Oswald (1980). Raw scores were calculated as the distance in mm of each mark from the left-hand margin of the 10cm line. Each subject's baseline week ratings were then averaged, and the standard deviation for this period was calculated. Each subsequent daily rating was then deducted from the baseline mean score, and then

expressed as a percentage of the baseline standard deviation. Thus, for the three drug treatments weeks, and for the withdrawal week, rating scores were calculated as:

$$\frac{\text{Baseline Week Mean Score - Subsequent Raw Score}}{\text{Baseline Week Standard Deviation}} \times 100$$

Using these transformed scores, the mean ratings for each of the three drug treatment weeks, and for the withdrawal week, were computed for each subject. These data were then analyzed using repeated measures analysis of variance with two trial factors, viz. drug (placebo; loprazolam 1.0mg; triazolam 0.5mg; and loprazolam 0.5mg) and week (week 1; week 2; week 3; and withdrawal), and one grouping factor, viz. age (those above the median age at the start of the experiment versus those below the median age at the start of the experiment). The main effects of, and interaction effects between these factors were computed. Where significant main effects of the drug factor, or significant interaction effects between the drug factor and the weeks factor were found, relevant within factor means were compared using correlated t-tests.

Additional analyses of Anxiety Ratings

Throughout the course of the study, nine further subjects participated in a separate, though similarly designed, sleep-laboratory investigation of the three experimental treatments

(loprazolam 1.0mg and 0.5mg, and triazolam 0.5mg). Each of these nine subjects completed daily ratings on visual analogue scales identical to those used in the present experiment. Drug treatments were taken for a period of three weeks, preceded by 14 nights, and followed by seven nights of placebo capsules. It was therefore possible to process, and to combine, subjective rating scores from the two experiments in a post-hoc analysis of data. In a further analysis of the subjective ratings of anxiety, the data were pooled from the two studies, and the effects of loprazolam 1.0mg and triazolam 0.5mg compared using a repeated measure analysis of variance with two trial factors, viz. drug and week, and one grouping factor, age. In order to maintain comparability with previous analyses, the nine further subjects were grouped above and below the median age of the 12 performance-study subjects, (i.e. 52y). For the combined 21 subjects, this grouping resulted in an older sub-group with n = 13, and a younger sub-group with n = 9.

Results

Sleep Quality. Results from the analysis of variance of subjective ratings of sleep quality are shown in Table 4:1. Ratings of sleep quality showed no main effect of drug, but did show a highly significant drug x week interaction effect ($F = 5.28$; $df = 3,30$; $p<0.001$). The drug treatment means for each week are shown graphically in Figure 4:1, and the results of paired comparisons between drug treatments for each week are shown in Table 4:2.

Table 4:1 Analysis of variance for subjective ratings of sleep quality

Source	Degrees of freedom	Sum of squares	Mean sum of squares	F-ratio
Age (A)	1	59949.36	59949.36	Ø.71
Error	1Ø	849983.92	84998.39	
Drug (D)	3	68160.13	22720.04	Ø.2Ø
D x A	3	103793.50	34597.83	Ø.31
Error	3Ø	3326723.35	110890.78	
Week (W)	3	1049042.48	349680.83	11.95**
W x A	3	139006.57	46335.52	1.58
Error	3Ø	878132.59	29271.09	
D x W	9	611186.27	67909.59	5.28**
D x W x A	9	223098.50	24788.73	1.93
Error	9Ø	1156841.18	12853.79	

* p<Ø.Ø5
** p<Ø.Ø1

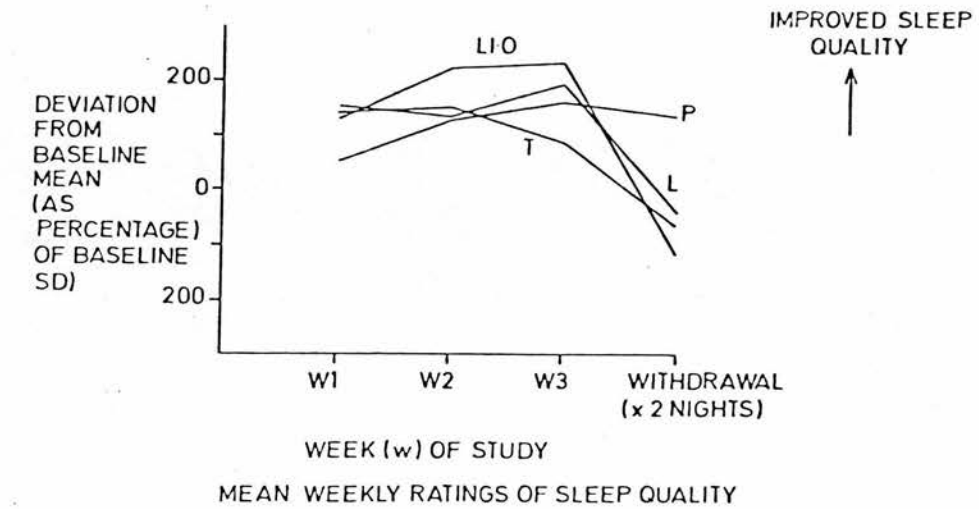


Figure 4:1 Effects of two hypnotics on subjective ratings of sleep quality

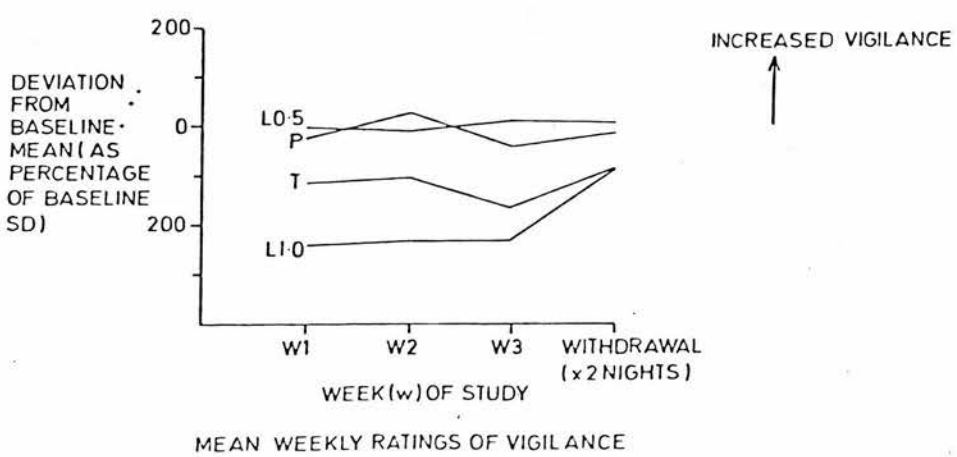


Figure 4:2 Effects of two hypnotics on subjective ratings of morning vigilance

Table 4:2 Mean weekly subjective ratings of sleep quality paired comparisons between drug treatments for each week

Week 1

Drug Treatment	(mean; SD)	v	Drug Treatment	(mean; SD)	t-value
LØ.1	(-132.21; 141.19)		P	(-47.94; 107.65)	1.43
T	(-128.11; 122.38)		P	(-47.94; 107.65)	1.85
LØ.5	(-140.02; 205.94)		P	(-47.94; 107.65)	1.21
L1.Ø	(-132.21; 141.19)		T	(-128.11; 122.38)	Ø.Ø9
L1.Ø	(-132.21; 141.19)		LØ.5	(-140.02; 205.94)	Ø.14
T	(-128.11; 122.38)		LØ.5	(-140.02; 205.94)	Ø.16

Week 2

L1.Ø	(-191.72; 240.91)		P	(-125.39; 191.76)	Ø.68
T	(-153.39; 190.35)		P	(-125.39; 191.76)	Ø.35
LØ.5	(-139.64; 151.79)		P	(-125.39; 191.76)	Ø.18
L1.Ø	(-191.72; 240.91)		T	(-153.39; 190.35)	Ø.48
L1.Ø	(-191.72; 240.91)		LØ.5	(-139.64; 151.79)	Ø.74
T	(-153.39; 190.35)		LØ.5	(-139.64; 151.79)	Ø.17

Week 3

L1.Ø	(-209.75; 195.38)		P	(-180.97; 275.49)	Ø.34
T	(-90.92; 217.65)		P	(-180.97; 275.49)	Ø.97
LØ.5	(-86.89; 184.40)		P	(-180.97; 275.49)	Ø.85
L1.Ø	(-209.75; 195.38)		T	(-90.92; 217.65)	1.88
L1.Ø	(-209.75; 195.38)		LØ.5	(-86.89; 184.40)	2.Ø1
T	(-90.92; 217.65)		LØ.5	(-86.89; 184.40)	Ø.Ø5

Withdrawal (x 2 nights)

L1.Ø	(125.36; 150.24)		P	(-127.93; 345.Ø2)	2.49*
T	(79.49; 148.43)		P	(-127.93; 345.Ø2)	2.41
LØ.5	(49.64; 102.Ø7)		P	(-127.93; 345.Ø2)	1.63
L1.Ø	(125.36; 150.24)		T	(79.49; 148.43)	1.Ø5
L1.Ø	(125.36; 150.24)		LØ.5	(49.64; 102.Ø7)	1.12
T	(79.49; 148.43)		LØ.5	(49.64; 102.Ø7)	Ø.51

* p<Ø.Ø5
** p<Ø.Ø1

t-values are for t (correlated), df = 11

Morning Vigilance. Results from the analysis of variance of subjective ratings of morning vigilance are shown in Table 4:3. Ratings of morning vigilance showed a significant main effect of drug ($F = 2.88$; $df = 3,30$; $p<0.05$) which was independent of both the week, and the age factors. The drug treatment means for each week are shown graphically in Figure 4:2. The results from paired comparisons of the overall drug treatment means are shown in Table 4:4a; the results from paired comparisons between the treatment means for each week are shown in table 4:4b.

Concentration. Results from the analysis of variance of subjective ratings of concentration are shown in Table 4:5. Ratings of concentration showed no significant main effects of drug, and no significant interaction effects between the drug and week, or between the drug and age factors. The drug treatment means are shown graphically in Figure 4:3.

Anxiety. Results from the analysis of variance of subjective ratings of anxiety are shown in Table 4:6. Ratings of anxiety showed a significant main effect of drug ($F = 3.49$; $df = 3,30$; $p<0.05$) which was independent of both the week, and the age factors. The drug treatment means for each week are shown graphically in Figure 4:4, and the results of paired comparisons between the overall drug treatment means are shown in Table 4:7a. Results from paired comparisons between the treatment means for each week are shown in Table 4:7b. It can be seen from Figure 4:4, and also from the paired comparisons shown in Table 4:7a, that the most extreme changes from baseline mean ratings were associated with triazolam 0.5mg, and loprazolam 1.0mg. Interestingly, while subjectively rated anxiety appeared to decrease during the loprazolam 1.0mg condition, triazolam 0.5mg was associated with a mean increase. To further investigate this

Table 4:3 Analysis of variance for subjective ratings of morning vigilance

Source	Degrees of freedom	Sum of squares	Mean sum of squares	F-ratio
Age (A)	1	27028.72	27028.72	0.15
Error	10	1863352.43	186335.24	
Drug (D)	3	1273817.39	424605.80	2.88*
D x A	3	394424.15	131474.72	0.89
Error	30	4423012.44	147433.75	
Week (W)	3	88646.16	29548.72	0.75
W x A	3	75203.74	25067.91	0.64
Error	30	1182445.99	39414.87	
D x W	9	172485.90	19165.10	0.75
D x W x A	9	384380.08	42708.90	1.68
Error	90	2291384.07	25459.82	

* p<0.05
** p<0.01

Table 4:4a Subjective ratings of morning vigilance: paired comparisons between the drug treatment means

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L0.1 (-197.99; 302.34)	P	(-15.10; 122.77)	1.77
T (-122.93; 166.88)	P	(-15.10; 122.77)	1.92
L0.5 (1.32; 134.61)	P	(-15.10; 122.77)	0.25
L1.0 (-197.99; 302.34)	T	(-122.93; 166.88)	0.82
L1.0 (-197.99; 302.34)	L0.5	(1.32; 134.61)	2.42*
T (-122.93; 166.88)	L0.5	(1.32; 134.61)	2.19*

* p<0.05
** p<0.01

t-values are for t (correlated), df = 11

Table 4:4b Mean weekly subjective ratings of morning vigilance: paired comparisons between the drug treatments for each week

Week 1

Drug Treatment	(mean; SD)	v Drug Treatment	(mean; SD)	t value
L1.Ø	(-239.26; 338.68)	P	(-25.49; 78.91)	2.15*
T	(-115.19; 239.74)	P	(-25.49; 78.91)	1.2Ø
LØ.5	(-1.15; 176.44)	P	(-25.49; 78.91)	Ø.43
L1.Ø	(-239.26; 338.68)	T	(-115.19; 239.74)	1.29
L1.Ø	(-239.26; 338.68)	LØ.5	(-1.15; 176.44)	2.59*
T	(-115.19; 239.74)	LØ.5	(-1.15; 176.44)	1.23

Week 2

LØ.1	(-229.42; 465.18)	P	(25.65; 95.11)	1.74
T	(-1Ø8.26; 254.Ø1)	P	(25.65' 95.11)	1.91
LØ.5	(-14.79; 221.72)	P	(25.65; 95.11)	Ø.58
L1.Ø	(-229.42; 465.18)	T	(-1Ø8.26; 254.Ø1)	Ø.82
L1.Ø	(-229.42; 465.18)	LØ.5	(-14.79; 221.72)	1.69
T	(-1Ø8.26; 254.Ø1)	LØ.5	(-14.79; 221.72)	1.23

Week 3

L1.Ø	(-23Ø.Ø2; 388.15)	P	(-41.5Ø; 235.25)	1.37
T	(-176.26; 25Ø.31)	P	(-41.5Ø; 235.25)	1.31
LØ.5	(17.Ø4; 19Ø.19)	P	(-41.5Ø; 235.25)	Ø.5Ø
L1.Ø	(-23Ø.Ø2; 388.15)	T	(-176.26; 25Ø.31)	Ø.43
L1.Ø	(-23Ø.Ø2; 388.15)	LØ.5	(17.Ø4; 19Ø.19)	2.12*
T	(-176.26; 25Ø.31)	LØ.5	(17.Ø4; 19Ø.19)	2.29*

Withdrawal (x 2 nights)

L1.Ø	(-93.27; 14Ø.45)	P	(-19.Ø6; 155.2Ø)	1.Ø7
T	(-92.Ø2; 165.2Ø)	P	(-19.Ø6; 155.2Ø)	1.5Ø
LØ.5	(4.22; 2Ø6.88)	P	(-19.Ø6; 155.2Ø)	Ø.27
L1.Ø	(-93.27; 14Ø.45)	T	(-92.Ø2; 165.2Ø)	Ø.Ø2
L1.Ø	(-93.27; 14Ø.45)	LØ.5	(4.22; 2Ø6.88)	1.47
T	(-92.Ø2; 165.2Ø)	LØ.5	(4.22; 2Ø6.88)	1.25

* p<Ø.Ø5
** p<Ø.Ø1

t-values are for t (correlated), df = 11

Table 4:5 Analysis of variance for subjective ratings of concentration

Source	Degrees of freedom	Sum of squares	Mean sum of squares	F-ratio
Age (A)	1	4042.41	4042.41	0.02
Error	10	2178384.71	217838.47	
Drug (D)	3	202471.69	67490.56	0.61
D x A	3	377156.15	125718.72	1.14
Error	30	3312012.57	110400.42	
Week (W)	3	33115.16	11038.39	0.33
W x A	3	35477.08	11825.69	0.36
Error	30	99037.21	33301.24	
D x W	9	330914.45	36738.27	0.95
D x W x A	9	219682.55	24409.17	0.63
Error	90	3491908.57	38798.98	

Table 4:6 Analysis of variance for subjective ratings of anxiety

Source	Degrees of freedom	Sum of squares	Mean sum of squares	F-ratio
Age (A)	1	61850.30	61850.30	0.61
Error	10	1020471.28	102047.13	
Drug (D)	3	690411.63	230137.21	3.49*
D x A	3	109646.75	36548.92	0.55
Error	30	1979547.29	65984.91	
Week (W)	3	142097.07	47365.69	1.96
W x A	3	782.22	260.74	0.01
Error	30	725796.99	24193.23	
D x W	9	303300.90	33700.10	1.81
D x W x A	9	191439.23	21271.03	1.14
Error	30	1674618.38	18606.87	

* $p<0.05$

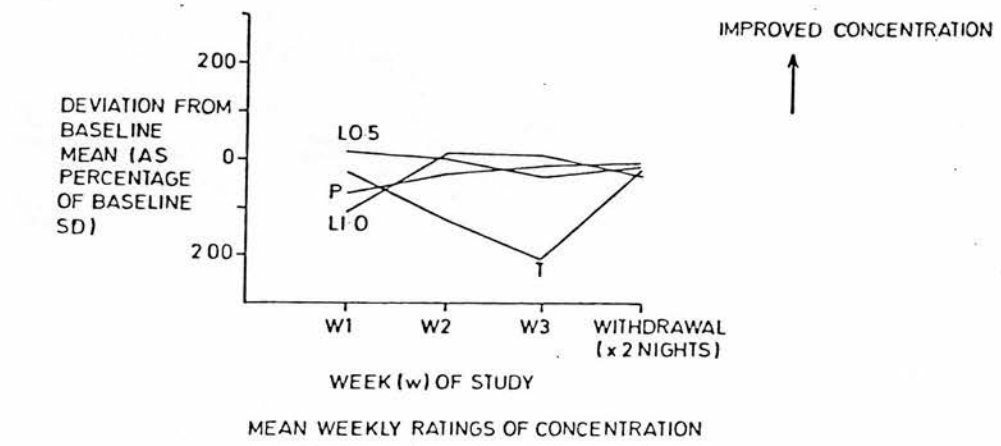


Figure 4:3 Effects of two hypnotics on subjective ratings of concentration

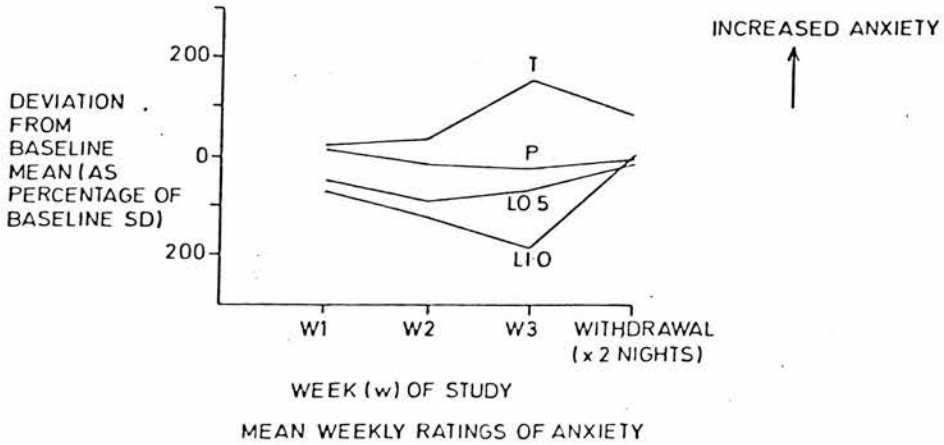


Figure 4:4 Effects of two hypnotics on subjective ratings of anxiety

Table 4.7a Subjective ratings of anxiety: paired comparisons between the drug treatment means

Drug Treatment	(mean; SD)	v	Drug Treatment	(mean; SD)	t-value
L1.Ø	(-86.93; 163.7Ø)		P	(-1.81; 93.91)	1.4Ø
T	(7Ø.89; 165.9Ø)		P	(-1.81; 93.91)	1.21
LØ.5	(-56.35; 94.55)		P	(-1.81; 93.91)	1.15
L1.Ø	(-86.93; 163.7Ø)		T	(7Ø.89; 165.9Ø)	4.83**
L1.Ø	(-86.93; 163.7Ø)		LØ.5	(-56.35; 94.55)	Ø.65
T	(7Ø.89; 165.9Ø)		LØ.5	(-56.35; 94.55)	2.32*

* p<Ø.Ø5
** p<Ø.Ø1

values are for t (correlated), df = 11

Table 4:7b Mean weekly subjective ratings of anxiety; paired comparisons between the drug treatments for each week

Week 1

Drug Treatment	(mean; SD)	v Drug Treatment	(mean; SD)	t-value
L1.Ø	(-77.76; 185.84)	P	(15.36; 9Ø.Ø2)	1.7Ø
T	(2Ø.22; 136.74)	P	(15.36; 9Ø.Ø2)	Ø.1Ø
LØ.5	(-51.8Ø; 126.34)	P	(15.36; 9Ø.Ø2)	1.52
LØ.5	(-77.76; 185.84)	T	(2Ø.22; 136.74)	1.74
L1.Ø	(-77.76; 185.84)	LØ.5	(-51.8Ø; 126.34)	Ø.43
T	(2Ø.22; 136.74)	LØ.5	(-51.8Ø; 126.34)	1.Ø3

Week 2

L1.Ø	(-125.ØØ; 17Ø.55)	P	(-17.45; 156.Ø3)	1.36
T	(35.2Ø; 14Ø.ØØ)	P	(-17.45; 156.Ø3)	Ø.83
LØ.5	(-9Ø.Ø1; 77.Ø5)	P	(-17.45; 156.Ø3)	1.31
L1.Ø	(-125.ØØ; 17Ø.55)	T	(35.2Ø; 14Ø.ØØ)	4.Ø2**
L1.Ø	(-125.ØØ; 17Ø.55)	LØ.5	(-9Ø.Ø1; 77.Ø5)	Ø.62
T	(35.2Ø; 14Ø.ØØ)	LØ.5	(-9Ø.Ø1; 77.Ø5)	2.54*

Week 3

L1.Ø	(-172.45; 278.81)	P	(-21.5Ø; 129.64)	1.51
T	(155.24; 368.Ø3)	P	(-21.5Ø; 129.64)	1.42
LØ.5	(-68.Ø9; 225.87)	P	(-21.5Ø; 129.64)	Ø.5Ø
L1.Ø	(-172.45; 278.81)	T	(155.24; 368.Ø3)	3.87**
L1.Ø	(-172.45; 278.81)	LØ.5	(-68.Ø9; 225.87)	1.12
T	(155.24; 368.Ø3)	LØ.5	(-68.Ø9; 225.87)	2.Ø2

Withdrawal (x 2 nights)

L1.Ø	(27.48; 1Ø9.Ø8)	P	(16.33; 135.7Ø)	Ø.22
T	(72.89; 146.3Ø)	P	(16.33; 135.7Ø)	Ø.99
LØ.5	(-15.49; 187.17)	P	(16.33; 135.7Ø)	Ø.45
L1.Ø	(27.48; 1Ø9.Ø8)	T	(72.89; 146.3Ø)	2.62*
L1.Ø	(27.48; 1Ø9.Ø8)	LØ.5	(-15.49; 187.17)	Ø.73
T	(72.89; 146.3Ø)	LØ.5	(-15.49; 187.19)	1.48

* p<Ø.Ø5
** p<Ø.Ø1

t-values are for t (correlated), df = 11

finding, anxiety ratings from the sleep laboratory study (described above) were pooled with the present data, and the effects of the two drug treatments were compared in a further analysis. The results from this additional analysis of the anxiety ratings are shown in Table 4:8. This analysis showed a significant difference between the two drug treatments ($F = 5.79$; $df = 1,19$; $p<0.05$), and also showed a significant drug x week interaction effect ($F = 3.81$; $df = 3,57$; $p<0.05$). The drug treatment means are shown graphically in Figure 4:5, and the results of paired comparisons between the two drug treatments for each week are shown in Table 4:9.

Discussion

Each subjectively rated variable will be considered in turn, and then discussed in relation to the performance data reported in the previous chapter.

Sleep Quality. For the three weeks of active drug consumption, mean weekly subjective ratings of sleep quality associated with triazolam 0.5mg, loprazolam 1.0mg, and loprazolam 0.5mg, showed no significant departure from placebo ratings (Table 4:2). Figure 4:1 shows a uniform tendency for subjects, on average, to rate their sleep as improved, even during the placebo condition. Mean scores for the withdrawal period, however, clearly distinguish between active drug, and placebo conditions.

Table 4:8 Analysis of variance for subjective ratings of anxiety. Data combined from sleep (n = 9) and performance (n = 12) subjects.

Source	Degrees of freedom	Sum of squares	Mean sum of squares	F-ratio
Age (A)	1	8324.14	8324.14	Ø.Ø4
Error	19	4199323.Ø9	221Ø17.ØØ	
Drug (D)	1	1Ø39997.13	1Ø39997.13	5.79*
D x A	1	36368.25	36268.25	Ø.2Ø
Error	19	3411539.76	179554.72	
Week (W)	3	156767.68	52255.89	1.59
W x A	3	15ØØ7.49	5ØØ2.5Ø	Ø.15
Error		1867885.33	32769.92	
D x W	3	321Ø81.26	1Ø7Ø27.Ø8	3.81*
D x W x A	3	9612.89	32Ø4.3Ø	Ø.11
Error	57	1599986.39	28Ø69.94	

* p<Ø.Ø5

Table 4:9 Mean weekly subjective ratings of anxiety. Data combined from sleep (n = 9) and performance (n = 12) subjects: paired comparisons between loprazolam 1.Ømg and triazolam Ø.5mg

Week 1

Drug Treatment (mean; SD)	v	Drug Treatment (mean; SD)	t-value
L1.Ø (-56.15; 147.Ø9)		T (38.88; 121.67)	2.48

Week 2

L1.Ø (-76.21; 152.43)		T (89.78; 249.59)	2.71*

Week 3

L1.Ø (-1Ø3.69; 232.45)		T (21Ø.8Ø; 474.Ø8)	3.ØØ**

Withdrawal (x 2 nights)

L1.Ø (15.87; 11Ø.61)		T (117.29; 38Ø.Ø3)	1.14

* p<Ø.Ø5
** p<Ø.Ø1

t-values are for t (correlated), df = 2Ø

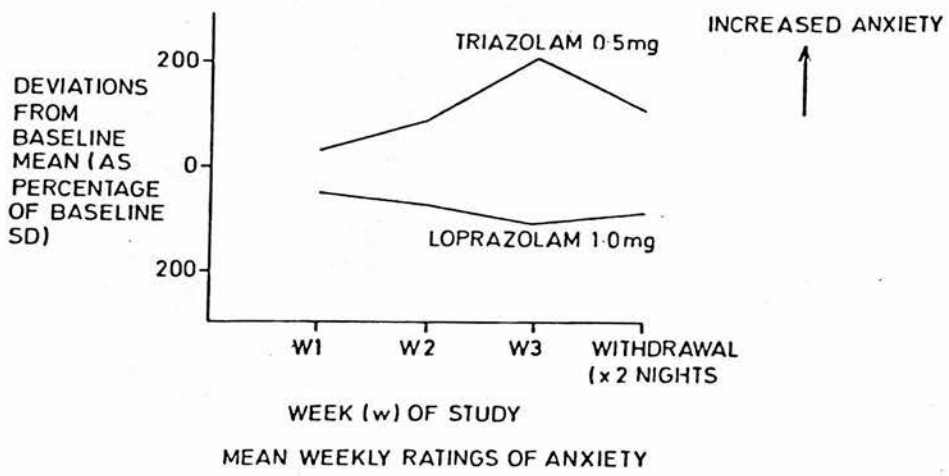


Figure 4:5 Effects of triazolam 0.5mg and loprazolam 1.0mg on subjective ratings of anxiety: combined data from sleep study (n = 9) and performance study (n = 12)

Withdrawal of both triazolam 0.5mg, and loprazolam 1.0mg was associated with significantly impaired sleep quality.

The tendency for subjects to rate their sleep as improved, relative to baseline, during the placebo condition clearly prevented significant differences emerging when active drug and placebo means were compared. Subjectively rated improvements in sleep quality have been reported by Hindmarch and Clyde (1980) for loprazolam 1.0mg, and by Roth et al. (1977) for triazolam 0.5mg. Reeves (1977) also reports that triazolam 0.5mg significantly improved subjective sleep quality over a 28 day period in a group of elderly hospital outpatients. Placebo scores in the present experiment, however, show no effect of withdrawal, while both triazolam, and loprazolam 1.0mg show withdrawal effects consistent with rebound insomnia, and typical of effective hypnotics, e.g. Allen and Oswald (1976); Oswald et al. (1979).

Morning Vigilance. While none of the active drug treatment means differed significantly from placebo (Table 4:4), ratings of morning vigilance during the triazolam and loprazolam 1.0mg conditions were significantly lower than those which obtained during the loprazolam 0.5mg condition. Comparing the mean values for each drug condition week-by-week (Table 4:4b), it can be seen that loprazolam 1.0mg was associated with reduced vigilance relative to both loprazolam 0.5mg and placebo in week 1, while week 3 comparisons again show significantly reduced vigilance for loprazolam 1.0mg and triazolam 0.5mg when compared with loprazolam 0.5mg. That the main drug effect shown in Table 4:3 is

independent of the Weeks factor confirms the impression given in Figure 4:2 of a sustained and consistent reduction in morning vigilance for the triazolam and loprazolam 1.0mg conditions (relative to loprazolam 0.5mg) throughout the drug-taking period. For the two-day withdrawal period, Figure 4:2 shows a tendency for ratings to return to baseline values.

Anxiety. Relative to placebo, subjects experienced no significant change in evening anxiety levels during the active drug treatments. Nevertheless, as Figure 4:4 shows, while both doses of loprazolam were associated with a mean decrease in anxiety, triazolam was associated with a mean increase. These mean differences between the loprazolam and triazolam conditions reached significance for both the lower (0.5mg) and higher (1.0mg) doses of loprazolam (Table 4:7a). Considered week-by-week, Table 4:7b also shows that significant differences between triazolam and loprazolam 1.0mg were sustained throughout the second and third weeks of consumption, and after two nights following drug withdrawal. Analysis of the data pooled from 21 subjects shows a similar pattern of significant differences between these two conditions, with triazolam consistently associated with increased anxiety relative to loprazolam 1.0mg during each week of consumption, but not two days after drug withdrawal.

A mean reduction in subjectively assessed anxiety is not a particularly surprising consequence of hypnotic drug usage. Oswald (1980) has pointed out that hypnotic drugs are also anti-

anxiety drugs, and that drugs used to modify anxiety states may also be used as hypnotics. Mean increases in anxiety, however, are more usually encountered on withdrawal of such medication after sustained usage (e.g. Allen and Oswald, 1976; Petursson and Lader, 1981). It would be parsimonious, therefore, to suggest that the relative increase in anxiety associated with triazolam in the present study is related to the withdrawal process.

The time-course of rebound phenomena associated with sedative-hypnotic drug withdrawal (e.g. insomnia, feelings of anxiety) appears to be closely related to the elimination half-life of the drug concerned. Allen and Oswald (1976) report that, in a group of six middle-aged subjects who had been taking fosazepam 60mg nightly for three weeks, visual analogue ratings of anxiety rose to a peak 3-4 days after withdrawal. The withdrawal profile reported by Petursson and Lader (1981) for 16 chronic benzodiazepine users (most of whom had been taking diazepam for more than one year) shows that peak anxiety, as measured by the Hamilton Rating Scale, occurred between 4 and 7 days. While both drugs produce the active metabolite N-desmethyldiazepam, diazepam remains active for up to 28h longer than fosazepam. Triazolam, on the other hand, is both short acting, and devoid of known active metabolic products. It is reasonable to conclude, therefore, that the rapid metabolism of triazolam 0.5mg lead, in the present experiment, to daytime rebound anxiety relative to the more characteristic reduction in anxiety associated with the longer acting loprazolam. Such a conclusion is consonant with clinical observations associating anxiety states with chronic usage of high

dose triazolam (van der Kroef, 1979).

Conclusions

In relation to the performance data considered in the previous chapter, it is clear that visual analogue ratings, while efficient at detecting drug-induced changes in mood and subjective feelings, are less efficient at predicting the effects of drug usage on performance. Unlike many of the performance tests, none of the subjective variables distinguished between the age sub-groups. It is relevant to note here that Castleden et al. (1977) found a similar insensitivity in subjective ratings. These authors report that, while performance measures differed significantly between old and young subjects following a single dose of nitrazepam 10mg, subjective ratings of sleep quality, daytime alertness, and side effects did not. Conversely, the effects of drug withdrawal in the present study, while absent from the performance data, are clearly visible in the ratings of sleep quality and morning vigilance; the significant reduction in sleep quality associated with the withdrawal of loprazolam 1.0mg and triazolam 0.5mg, for example, were not associated with measurable effects on objective measures of performance.

While the subjective ratings used in the present experiment

did not predict the outcome of objective performance tests, they do provide an important aid to the interpretation of performance test data. This is, perhaps, best illustrated by the relationship, already discussed, between objective and subjective measures of daytime vigilance. The subjective ratings of anxiety might similarly clarify the (rather isolated) differences betweeen triazolam and loprazolam seen in the performance results. On the auditory vigilance task, for example, the older sub-group made significantly more false positive reports during the triazolam condition than during the loprazolam 0.5mg condition, at the 16.30 testing session on week three (see Table 3:4). If relative increases in anxiety occurred as a daytime rebound phenomenon, then it is likely that the evening (16.30) testing sessions would have been most sensitive to these changes in mood and motivation. Figures 3:4a, 3:4b, and 3:4c show that, for the older sub-group, while false reports increased under triazolam at all times of testing on week three, the greatest increase occurred in the evening. The differential effects of triazolam and loprazolam on subjective feelings of anxiety, therefore, may have contributed to the significant drug x week x time x age interaction shown in Table 3:1 for false positive reports.

Chapter 5

Increased susceptibility to the adverse behavioural consequences of hypnotic drug use in the elderly: A review of the clinical, epidemiological and experimental literature.

The experimental data presented in the previous two chapters showed little evidence of differential drug effects on performance between early and late middle-aged subjects. Evidence that the elderly (defined here as the age group 65y+) are more susceptible to the adverse behavioural effects of hypnotic drugs comes from a variety of sources, which include clinical observations, epidemiological surveys, and laboratory investigations. The present chapter examines this evidence and, in particular, focusses upon: 1) the testing strategies used to assess post hypnotic performance deficits in older subjects; and 2) relevant factors which appear greatly to affect the drug-performance relationship in the elderly. The latter part of this review provides the rationale for Experiment 2 (Chapter 8) and has two specific objectives. First, to identify aspects, and parameters, of performance in the elderly most consistently reported to be affected by hypnotic drugs. And second, to consider, with regard to the present literature, appropriate testing procedures to detect post-hypnotic performance decrements in the elderly. In many of the experimental studies considered, both pharmacokinetic and objective performance data have been reported. Greater emphasis will be placed here on performance data. Reviews of the pharmacokinetics in the elderly of psychotropic drugs in general, and hypnotic drugs in particular, have been compiled by Hicks et

al. (1981) and Swift (1982) respectively.

Clinical Observations

Over the last decade both clinical observations and experimental studies have identified behavioural problems arising from hypnotic drug usage which appear to be specific to the elderly. Evans and Jarvis (1972) report a confusional state in elderly patients associated with the chronic use of nitrazepam. This syndrome, which diminished rapidly on withdrawal of the drug, presented a clinical profile similar to dementia. Similar pseudo-dementias have been attributed to long term bromide and barbiturate use in the elderly (Rudd, 1972), with equally rapid reversal of symptoms on withdrawal.

Further evidence of benzodiazepine toxicity specific to the elderly is provided by information from the Boston Collaborative Drug Surveillance Program (BCDSP), an extensive, multi-national survey of hospital admissions sampled from 1969 onwards. Reports originating from this source show the frequency, and the severity, of residual "central nervous system depression" (i.e. clinically assessed drowsiness, ataxia, and hangover) to be consistently and significantly greater in the age group 70y+ following diazepam (BCDSP, 1973), chlordiazepoxide (BCDSP, 1973), flurazepam (Greenblatt, Allen and Shader, 1977), and nitrazepam (Greenblatt and Allen, 1978). As regards nitrazepam and flurazepam, the probability of drug-age interactions were reported to increase with the dose of the drug (Greenblatt, Allen and Shader, 1977; Greenblatt and Allen, 1978).

Controlled clinical evaluations of hypnotic drug effects also emphasize the susceptibility of elderly hospital inpatients to adverse behavioural reactions, particularly in those individuals with pre-existing mental impairment. Harenko (1975) compared the hypnotic efficacy of chlormethiazole 500mg and nitrazepam 10mg in 68 demented psychogeriatric patients (mean age = 77y). Only 44 patients completed the seven-day crossover study. Of the remaining 24, 16 discontinued because of "severe 'hang-over' effects" (mostly associated with nitrazepam), and in a further five patients who did complete the study, observers reported a "worsening of the patients' mental condition" (associated exclusively with nitrazepam). Similar drug comparisons in psychogeriatric populations have reported equally profound behavioural disturbances. Linnoila and Viukari (1976), comparing 14 consecutive nightly doses of nitrazepam 10mg and thioridazine 25mg in a crossover study with 20 such patients report that "ability to move declined drastically in 8 patients, and slightly in 2 during the nitrazepam condition". General "ability to conduct daily activities" was also reported to be impaired in 9 patients during the nitrazepam condition, compared with only 3 following thioridazine. The authors concluded that nitrazepam should "probably be avoided in the treatment of psychogeriatric patients". Elderly hypnotic users in the community have received relatively less clinical attention, and evidence of drug-associated behavioural impairment in this population is largely indirect. Macdonald and Macdonald (1977a), for example, report that, of 390 patients admitted to a geriatric-orthopaedic unit

following nocturnal femoral fractures (due to falls), over 90% were receiving barbiturate hypnotics at the time of the accident. A significant proportion of these barbiturate users were subsequently described as having "a clinically important degree of mental confusion" (Macdonald and Macdonald, 1977b). In a survey of 1998 patients consecutively admitted to geriatric medical units, Williamson and Chopin (1980) list adverse reactions to "hypnotics, sedatives, and anticonvulsants" as the main factor contributing to admission in a minority of cases.

These clinical, and controlled, observations indicate that hypnotic drugs can produce behavioural deficits in the elderly which are not apparent, or do not occur, in younger age groups. Considerably less emphasis, however, has been placed on systematically evaluating these deficits. Controlled clinical trials of hypnotic drugs using elderly hospital patients have relied heavily on nurse ratings of both hypnotic efficacy, and residual sedation. While nurse ratings of sleep variables (e.g. onset latency, duration, continuity, etc.) are known to be extremely unreliable in some patients (Kupfer et al. 1970; Weiss et al. 1973), subjective evaluations of 'hangover effects' have produced conflicting results. Pathy (1975), for example, compared the hypnotic efficacy and residual effects of chlormethiazole (base) 384mg, dichloralphenazone 1.3G, and placebo nightly for seven night in 38 geriatric patients. Nurse ratings showed no significant residual effects during either of the active treatments. Middleton (1978), on the other hand, comparing chlormethiazole (edisylate) 500mg with temazepam 10-20mg, reports

both drugs, but particularly chlormethiazole, to be associated with early morning drowsiness and increasing confusion over a seven day period, in a group of 56 medical geriatric patients. Again, these conclusions were based on nurse ratings. This apparent unreliability in subjective methods of quantifying the effects of the same hypnotic drug (in this case, chlormethiazole) emphasizes the need for, and the value of, objective measures of performance efficiency.

In a recently reported study, Murphy et al. (1982) combined nurse ratings and objective performance measures in a repeated dose study of nitrazepam and triazolam. In this trial, the effects of five consecutive nightly doses of nitrazepam 2.5mg, and triazolam 0.125mg were assessed in 16 geriatric inpatients. A between groups design was used (n = 8/group), and subjects were tested on four occasions: pre-drug (baseline); after one dose; after five consecutive doses; and post drug. No placebo control was included. Performance was assessed on a card sorting task (similar to that described in Chapter 2). The authors concluded that nitrazepam, but not triazolam, significantly impaired processing time on the morning following the fifth dose. This conclusion is supported only by paired comparisons, made within each group, between pre-drug and fifth drug-dose test scores (neither the test used, nor the statistic derived is reported). It <u>is</u> evident from the data provided in this report, however, that the mean baseline processing time for the triazolam group (19.5sec) was almost twice that of the nitrazepam group (10.5sec). The discrepancy between these scores considerably reduces the

probability of baseline versus drug-score comparisons achieving significance for the triazolam group. With regard to Philips' (1977) observations (described below), the conclusions of Murphy et al. (1982) would have been more appropriately supported by the demonstration of a significant Group (nitrazepam/triazolam) by Occasions (pre-drug/dose 1/dose 5) interaction following a repeated measures analysis of variance.

Experimental Performance Studies

Few studies have attempted objectively to measure performance in the non-hospitalized elderly, and few of these have compared the post-drug performance of elderly and young subjects. Studies which have reported objective performance measurement and age group comparisons will be considered in some detail. In a single dose study, Castleden et al. (1977) compared the performance of healthy elderly (mean age = 74.7y) and young adult (mean age = 23.3y) subjects on a simple letter cancellation task following nitrazepam 10mg and placebo. Elderly subjects made significantly more errors on the test than did the young up to 36h after drug administration. Motor performance, however, as judged by time-on-task, and subjective ratings of alertness, as measured by 10cm visual analogue scales, were reported to be similarly impaired in both groups. The plasma elimination half-life of nitrazepam also showed no significant difference between the groups (mean half-lives: elderly group = 32.5h; young group = 32.0h). These authors

concluded, therefore, that their data indicate a pharmacodynamic interaction between nitrazepam and the ageing brain.

A similar conclusion is reported by Swift et al. (1980). In this study, the performance of nine healthy elderly (age range = 68-79y) and young adult (age range = 20-27y) subjects was compared 0.5, 2, 4, and 11 hours after a single morning dose of temazepam 20mg. Performance indices included critical flicker fusion threshold (CFFT), choice reaction time (CRT), and postural sway (as measured by Wright's ataxiameter). Relative to the younger group, older subjects were reported to be significantly more impaired on the sway test, CFFT, and CRT measures up to 6h, 11h, and 0.5h respectively following temazepam. In a similarly designed study, and using the same objective measurements of performance, Hockings et al. (1982) compared the effects of dichloralphenazone 1.3G, and chlormethiazole 384mg (base) in groups of 10 healthy elderly (mean age = 72.0y), and 10 healthy young (mean age = 23.0y) subjects. Following chlormethiazole, older subjects were reported to be relatively more impaired than the young on tests of postural sway, CRT, and CFFT 2.0h after ingestion. Dichloralphenazone increased postural sway in the elderly group 0.5h after ingestion, but had no other significant effect on measured performance. Neither drug was associated with residual effects after 4h. The authors concluded that chlormethiazole 384mg shows an "accentuated, immediate response" in the elderly relative to younger individuals.

In connection with Castleden et al.'s (1977), Swift et al.'s

(1980), and Hockings et al.'s (1982) conclusions, it is relevant to note actuarial considerations concerning group x treatment interactions. Philips (1977) argues that where two experimental groups (e.g. old/young) are subjected to two treatment conditions (e.g. drug/placebo), the conclusion that a given treatment affects one group relatively, and significantly, more than it does the other demands the demonstration of a statistically significant F-ratio for the treatment x group interaction. It is not an adequate basis for concluding such an interaction if significant differences from baseline are observed independently in one group, but not in the other. Neither Castleden et al. (1977), nor Swift et al. (1980) report significant drug x age interaction effects. Indeed, in neither study are analysis of variance data reported at all. In both cases, then, the conclusion of a drug x age interaction is not adequately supported.

While subjective assessments of post-drug behavioural efficiency may be unreliable, studies employing objective performance measures, such as those just considered, have also reported equivocal results. Briggs et al. (1980) examined the effects of temazepam 20mg, chlormethiazole 384mg, and placebo in 10 old (mean age = 72.9y) and 10 young (mean age = 24.7y) healthy female volunteers. Performance was assessed 4h and 11h after a single night-time dose of each treatment using subjective ratings, a measure of postural sway (using an ataxiameter), and a letter cancellation task (similar to that used by Castleden et al. [1977], but timed over a two minute period). No significant differences were found between the groups on subjective estimates

of sedation, postural sway, or psychomotor performance (as measured by the cancellation task). The authors concluded, therefore, that neither drug causes "...detectable hangover effects", a conclusion at odds with the findings of Swift et al. (1980) for an identical drug regime (single dose temazepam 20mg), and an identical measurement (postural sway).

Two possible factors, either alone, or in combination, may have contributed to these conflicting results. The first of these factors is specific to the design of Briggs et al.'s (1980) study, and the second concerns subject-variables pertinent to the testing of elderly individuals. First, for each treatment condition in Briggs et al.'s study, measures of performance, postural sway, and subjective state were obtained at 02.00, and 09.00 (i.e. 4h and 11h) after administration. Thus, placebo scores, against which both active drug treatments were compared, may have confounded with the effects of disturbed sleep, and may not have represented true baseline values. It is reasonable to suggest that, if placebo scores were depressed as a result of sleep disturbance, differences between drug and placebo conditions might have been diminished.

The second factor concerns possible differences in the characteristics of the elderly groups used by Briggs et al. (1980) and by Swift et al. (1980). Hicks (1981), reviewing the pharmacokinetics of psychotropic drugs in the elderly comments "...the ageing process varies from individual to individual, and from one organ system to another within the same individual.

Therefore, the concept of the 'geriatric' individual as a homogeneous entity, demarcated by some age-related cutoff line, is simplistic". Age alone, then, is not necessarily the only, or even the best, predictor of increased sensitivity to hypnotics in elderly individuals. Two further parameters which predict sensitivity are implicated in the current literature, viz. sex, and health status. Before considering these factors in detail, it is relevant to note here that Briggs et al.'s subjects were all female and "were apparently in good health", while Swift et al. used a mixed group, the health status of which was not reported.

Individual Differences

Sex differences in hypnotic drug effects on performance in the elderly have been reported by Salem et al. (1982). In this study, single doses of nitrazepam 10mg, or temazepam 20mg were administered, according to a crossover design, to 18 elderly individuals (nine males and nine females) whose ages ranged from 62-72y. Performance, as measured by two flash fusion threshold, simple reaction time, digital copying, a symbol digit modalities test, and the Gibson spiral maze, was assessed at 1, 2, 3, 4, 7, 9 and 11h after administration. The elimination half-lives of both drugs were also assessed. The results showed that the detrimental effects of nitrazepam (mean half-life: males = 43.2h; females = 32.9h) were greater in both magnitude and duration than those associated with temazepam. Within the nitrazepam condition, however, impairment on simple reaction time, digit copying, and the Gibson spiral maze (time and errors) persisted longer in

females, even though the estimated mean elimination half-life of nitrazepam was over 10h longer in males. Only one test, symbol digit modalities, showed a more persistent effect of nitrazepam in males than in females. The authors concluded, therefore, that sex differences in performance "cannot be explained by pharmacokinetics". These apparent sex differences in drug sensitivity may, however, simply reflect further, and, in terms of drug effects, influential differences between older males and females rather than sex per se (e.g. sex differences in physical health status, body weight, or competitiveness, etc.). Nevertheless, the sex of subjects remains a relevant consideration.

The influence of health status on drug-performance relationships in the elderly has not been specifically evaluated. Several reports, however, have identified aspects of general health status which appear to increase sensitivity to hypnotic drugs. Evans and Jarvis (1972), for example, refer to the " 'unmasking' of old cerebral damage" by repeated doses of nitrazepam (in the case study described by these authors, the 'unmasked' symptoms included hemiparesis and disorientation, both of which subsided on withdrawal of the drug). Similar observations have emerged from controlled clinical trials. Viukari et al. (1978) compared the effects of flurazepam 15mg, nitrazepam 5mg, and fosazepam 60mg on the daytime performance of 17 psychogeriatric inpatients. A balanced crossover design was used, and performance was measured on tests of memory, handgrip, and tapping speed. None of the treatments significantly affected

memory or handgrip strength in most patients, and only fosazepam and nitrazepam significantly reduced tapping speed (these results will be considered in greater detail later). However, two patients "with evident cerebrovascular disease" were profoundly affected by all three drugs, particularly on the memory tasks.

Specific examples of interactions between hypnotics and physical health status are reported in the clinical literature. The tendency for some hypnotics to exacerbate existing respiratory diseases has been reported by Clark et al. (1971), who describe three patients whose respiratory failure worsened following nitrazepam 5mg (1 case) and 10mg (2 cases). In a controlled double-blind trial Gaddie et al. (1972) report that nitrazepam 10mg reduced the ventilatory capacity of six patients with obstructive chronic bronchitis; forced vital capacity, and forced expiratory volume/second were significantly reduced 2h after drug administration. This study also reported a tendency for arterial oxygen tension to fall, and for hypercapnia to increase, after nitrazepam. Impairment of effective cerebral oxygenation has far reaching implications for the mental competence of elderly individuals who, by virtue of ageing alone, appear to show increased sensitivitiy to this particular drug (q.v. Castleden et al. 1977).

[It is interesting to note that these studies showing the interaction of hypnotic drugs with physical disease processes admit the possibility that, in some elderly individuals, hypnotic drugs may affect behavioural efficiency only indirectly. A

further example concerns exercise. Early morning sedation, and concomitant reductions in arousal, may tend to encourage periods of decreased motor activity or, at worst, lethargy. It has been demonstrated that physical fitness in the elderly, as measured by activity levels (Spirduso, 1975; Spirduso and Clifford, 1978), or by predicted VO2 max (Tredway, 1978), correl ates positively and significantly with the efficiency of psychomotor performance. An hypnotic which affects activity level and, by inference, general fitness, may also indirectly affect performance; see Spirduso (1980) for review.]

Clearly, between-subject differences in older age groups can contribute substantially to variable and heterogenous experimental results. The need for replicable, clinically relevant experimental data, therefore, requires that particular care is taken in the selection of elderly experimental subjects. Few studies employ objective selection criteria. Of the four experimental studies involving non-hospitalized subjects so far considered (Castleden et al. 1977; Briggs et al. 1980; Swift et al. 1982; and Salem et al. 1982) none employed objective assessments of cognitive status as selection criteria for subjects.

Testing strategies for assessing drug effects in the elderly

From the clinical observations reported above, it is plausible to suggest a spectrum of behavioural decrements in the elderly arising from hypnotic drug use, and ranging in severity from mild residual sedation (e.g. Greenblatt and Allen, 1978), to

gross pseudo-dementia (e.g. Evans and Jarvis, 1972). Existing mental or physical impair ment appears to increase vulnerability. This clinical profile suggests that the effects of hypnotic drugs interact with existing age-dependent reductions in behavioural efficiency and amplify the effects of abnormal - and possibly normal - ageing processes. It should be remembered, however, that much of this evidence is derived from hospitalized populations, and, with particular regard to the more severe behavioural deficits, does not necessarily generalize to healthy elderly populations. [Differences in the rate of clearance and the volume distribution of hypnotic drugs have been reported between healthy, and non-healthy elderly individuals. While Castleden et al. (1977) found no significant pharmacokinetic differences between healthy elderly and young subjects following nitrazepam 10mg, Iisalo et al. (1977), comparing sick elderly and healthy young subjects, report significant differences in the mean half-life (old = 40.4h; young = 28.9h) and the volume distribution (old = 4.8 l/kg; young = 2.4 l/kg) of single-dose nitrazepam 5mg.] Experimental studies which have reported post-drug performance decrements in the elderly will now be considered in greater detail, with the intention of identifying parameters of performance likely to be influenced by hypnotics in this age group.

Most of the experimental interest in post-hypnotic performance in the elderly has been concerned only with the presence or absence of decrements and, in the event, little attention has focussed on the aspects of psychological functioning

actually impaired. Such an approach is reflected in both the detail, and the emphasis of reported results, which, in general, emphasise characteristics of the drugs used, rather than those of the performance measured. Consequently, although there are comparatively few experimental studies concerning hypnotic drug effects on performance in the elderly, the wide variety of test procedures used makes direct comparisons between these studies problematical. An indirect approach to comparing these studies is shown in Table 5:1. A common feature of many of the tasks used is that the dependent variable measured reflects the speed, or the accuracy, of performance. Table 5:1 shows the residual effects of a variety of hypnotic drugs on these parameters of performance in the elderly. As several studies included testing sessions shortly after the administration of drug (i.e. the assessment of acute effects) "residual" effects are defined here as performance decrements measured not less than six hours after drug administration.

Speed appears to be the most consistently measured, and the most consistently impaired, parameter of performance. Simple tapping speed, as measured by the frequency of taps/min with the palm of the preferred hand, was consistently impaired in psychogeriatric patients following seven consecutive doses of nitrazepam 10mg (Linnoila and Viukari, 1976) and 5mg (Viukari et al, 1978), and fosazepam 60mg (Viukari et al. 1978). Thus, it appears that, at least in mildly demented individuals, these drugs can affect the efficient execution of repetitive motor responses which are largely independent of information processing,

Table 5:1 Residual effects of hypnotic drugs on the speed and accuracy of performance in the elderly

Study	Test	Drug	Results: speed	Results: accuracy
Linnoila & Viukari (1976)p	tapping speed	N 10mg	impaired	-
		Th 25mg	n.s.	-
Castleden et al. (1977)h	letter cancellation	N 10mg	impaired	impaired
Viukari et al. (1978)p	tapping speed	N 5mg	impaired	-
		Fl 15mg	n.s.	-
		Fo 60mg	impaired	-
Swift et al. (1980)h	choice reaction time	T 20mg	n.s.	-
Briggs et al. (1980)h	letter cancellation	Ch 384mg	-	n.s.
		T 20mg	-	n.s.
Salem et al. (1982)h	Gibson spiral maze	N 10mg:		
		(males)	n.s.	impaired
		(females)	impaired	impaired
		T 20mg:		
		(males)	n.s.	n.s.
		(females)	n.s.	n.s.
	simple reaction time	N 10mg		
		(males)	impaired	-
		(females)	impaired	-
		T 20mg		
		(males)	impaired	-
		(females)	impaired	-
Murphy et al. (1982)g	information processing time	Tr 0.125mg	n.s.	-
		N 2.5mg	impaired	-
Hockings et al. (1982)h	choice reaction time	Dp 1.3G	n.s.	-
		Ch 384mg	n.s.	-
Cook et al.** (1983)g	letter cancellation	T 20mg	impaired	n.s.
		N 5mg	impaired	n.s.
	choice reaction time	T 20mg	impaired	-
		N 5mg	impaired	-

N (nitrazepam); Th (thioridazine); Fl (flurazepam); Dp (dichloralphenazone); Fo (fosazepam); T (temazepam); Ch (chlormethiazole); Tr (triazolam).

g = geriatric patients; p = psychogeriatric patients;
h = healthy elderly subjects

or decision making, skills. Speed of performance which is dependent upon these skills (as in simple and choice reaction time tasks) has also been shown to be impaired in healthy elderly subjects, but not in young adult subjects, following single dose temazepam 20mg (Salem et al. 1982). Impairment of simple reaction time in healthy elderly subjects following nitrazepam 10mg is also reported by Salem et al. (1982).

Where speed and accuracy of performance have been measured from the same task, the results are less straightforward. In such tasks (e.g. the Gibson spiral maze; Castleden et al.'s [1977] letter cancellation test), efficient performance demands a "trade-off" between speed and accuracy, i.e. careful progress, though resulting in lower error scores, increases the time taken to complete the task, while faster performance increases the likelihood of errors. Instructed to work as quickly, and as accurately as possible, subjects select their own criterion of optimal performance. Castleden et al. (1977) required subjects to delete all the letter "e"s from a fixed-length page of prose. The number of non-"e"s deleted represented the error score. Healthy elderly subjects took significantly longer to complete the test, and made significantly more errors, 12 and 36h after nitrazepam 10mg, than they did 12 and 36h after placebo. Younger subjects, however, although taking significantly longer to complete the test after drug, did not make significantly more errors relative to their own baseline performance (as already mentioned above, the implicit assumption of a statistically significant drug-age interaction is not explicitly reported in this paper). Under the

drug condition, then, it would appear that younger subjects maintained previous levels of accuracy by reducing speed, whereas the older subjects failed to compensate for reduced accuracy despite significantly slower performance. Castleden et al. (1977) interpret these results as evidence for a central interaction between nitrazepam and the ageing brain. Certain aspects of this interpretation, however, may not be entirely justified.

Castleden et al. (1977) base their conclusion of a central interaction between nitrazepam and the ageing brain on the assumption that motor performance and cognitive efficiency were independently measured by the letter cancellation procedure. This, in turn, comprises two further assumptions: 1) that the data derived from the test reflect two discrete and independent processes which; 2) vary independently accross age ranges. While the first of these assumptions may be valid for younger age groups, it is unlikely to be valid for the elderly. Evidence from studies concerned with the speed of performance in the elderly suggest that, in older subjects, unlike their younger counterparts, central processing ability (or cognitive efficiency) and motor speed are intimately linked, and cannot be considered as independently varying. Birren (1965), reviewing such studies, comments "Young people tend to add and write at independent speeds whereas older people are jointly slow in both tasks...the correlation between writing and addition speeds indicates that one may not assume independence of output time (writing) and association time (addition) in the ageing as in the

young. These times grow interdependent with the age of the subject". Contrary to Castleden et al.'s (1977) assumptions, therefore, it would appear that speed of performance in the elderly may vary as a function of either the "central" or the "motor" effects of hypnotic drugs. Castlden et al.'s conclusion also makes a further assumption: that the psychological processes mediating performance on a given task are the same in the old and the young, and that, between age groups, these processes are equally robust. If, however, the elderly employ different, and perhaps more vulnerable cognitive strategies than the young, then these behavioural differences might also contribute to any apparent differential sensitivity to drug effects. Some relevant characteristics of performance in the elderly will briefly be considered.

Reduced speed of responses characterizes performance in the elderly. This reduction in speed is mediated by both physical and psychological factors. Among the psychological changes which contribute to slower performance in the elderly, Welford (1980) emphasises the tendency for older subjects to monitor their own responses in continuous performance tasks. Given a series of signals and appropriate responses (e.g. letter "e"s and their deletion) attention paid to the previous response will detract from that required to recognize the next signal. Thus, both the previous response and the subsequent signal compete for attention in older subjects, increasing the time taken to complete the task relative to younger individuals. This tendency for older adults closely to monitor their own movements during a response, to the

exclusion of immediate attention to new signals, has been reported in several experiments (e.g. Rabbit and Rogers, 1965; Rabbit and Birren, 1967). Speed of performance in the elderly, then, is determined not only by reduced efficiency in effector organs, but also by the cognitive strategy employed during a given task.

The efficient monitoring of performance also plays an important role in the trade-off between speed and accuracy. Achieving an optimal compromise between these two parameters requires sensitivity to, and efficient use of continuous feedback from test performance (Fitts and Posner, 1973). For example, a percieved increase in errors will influence the degree of caution exercised by the subject, resulting in a compensatory reduction of speed. Thus, the the efficiency of the subject's judgement during the task will greatly determine that individulal's efficiency on the task. It is particularly interesting to note, therefore, that Salem et al. (1982) report that, in their male subjects, nitrazepam 10mg significantly impaired accuracy, but not speed, on the Gibson spiral maze. This finding suggests the possibility that, at least in some elderly individuals, the efficient monitoring of performance, as suggested by the absence of compensatory speed reductions, may be impaired by hypnotic drugs. Both the recognition, and the appropriate use made of feedback cues from performance involve many different processes, including sensory perception, proprioception, and motivation. Impairment of each, or all, of these processes by hypnotics may result in poorly monitored, less accurate, performance which, nevertheless, continues at the same, or similar, speed. This

consideration is not without ecological validity. Such impairment would have implications for the ability of the elderly to recognize, and execute evasive action to avoid, the risk of everyday accidents.

Methodological considerations relevant to the testing of elderly subjects

Test Factors. While the Gibson spiral maze, as used by Salem et al. (1982), and the letter cancellation task, as used by Castleden et al. (1977), both yield measures of the speed and accuracy of performance, they differ in at least one influential characteristic, viz. the amount of irrelevant material presented in each task. Relative to younger individuals, the elderly demonstrate less ability to discriminate between relevant, and irrelevant material - a further source of reduced speed of response in this age group. Rabbit (1965), for example, required elderly (65-74y) and young (17-24y) subjects to sort cards according to certain criterion letters printed on each. The addition of irrelevant letters to each card produced greater slowing of performance in the elderly than in the young. Welford (1977) suggests that, in the elderly, such irrelevant material effectively weakens the "strength" of the target signal. Applied to Castleden et al.'s (1977) letter cancellation task, non-"e" characters in the prose would be irrelevant, detracting from, and weakening the stimulus impact of target "e"s, thus providing a further, and perhaps confounding, source of both slower, and less

accurate performance relative to younger subjects. Indeed, under these circumstances, it would be an appropriate further analysis to examine the degree to which letters deleted in error approximated the letter "e" (i.e. in terms of closed loops and angles, open loops and angles etc.). In order, therefore, simply to assess speed and accuracy of performance in the elderly, tests which present unspecified amounts of irrelevant matter are probably best avoided.

Design Factors. It has been noted (Rabbit, 1982) that laboratory test performance in the elderly is frequently suppressed by the anxiety and stress engendered by the testing situation itself. As these anxieties diminish with repeated exposure to the test situation, practice effects tend to be greater among the elderly than among the young (Rabbit, 1980). It also follows from this that the performance of younger subjects will "plateau" earlier than that of older subjects. These findings have two important implications for the design of psychopharmacological experiments for older subjects. First, relative to younger subjects, the elderly will require more practice sessions to adapt to the testing procedures, and achieve steady-state levels of performance. Second, if, relative to younger subjects, performance in the elderly is suppressed by test-associated anxiety, then performance in this group is likely to be more profoundly affected by residual anxiolytic drug activity. Unless older subjects are thoroughly adapted to the testing procedures, such an anxiolytic effect could confound with any detrimental residual effects. Indeed, it is possible that a drug

with anxiolytic activity may produce an apparent facilitation of performance in the elderly.

With regard to both these points, it is interesting to note that none of the studies shown in Table 5:1 report any adaptation or practice test sessions for young or old subjects. Murphy et al. (1982), for example, report that data derived from the first testing session were used as baseline measures.

Conclusions

Clinical and controlled observations, epidemiological surveys, and experimental studies show that the elderly, relative to younger age groups, are more likely to experience the untoward behavioural consequences of hypnotic drug usage. Experimental evaluations could provide a means for predicting the degree of behavioral risk associated with different hypnotic drugs in elderly patients. From the experimental studies examined, it is apparent, however, that their exists no consensus as to: 1) which aspects of performance should be measured for drug effects, or 2) which aspects of performance are most vulnerable to drug effects in the elderly. Evidence that some drugs may affect both speed and accuracy, or accuracy alone, provides a point of departure for further, more detailed, analyses of hypnotic drug effects on these parameters of performance in the elderly. The design of, and the tasks selected for, such analyses should take into consideration factors known to be relevant to the psychological testing of elderly individuals. Finally, criteria

used to select the experimental groups should ensure some degree of homogeneity as regards both the mental, and physical health status of elderly subjects, such that results may reasonably be generalized to similarly defined populations.

The clinical relevance of behavioural side effects in the elderly arising from the use of sedative-hypnotic drugs is, of course, proportional to the actual extent to which these drugs are prescribed for, and used by, elderly individuals. In the next two chapters, the residual effects of hypnotics in the elderly are considered in relation to the epidemiology of these drugs. It is the intention of both chapters to place the results from laboratory performance studies into the relevant context of the prescribing and use of sedative-hypnotic drugs among the elderly.

** The study by Cook et al. (1983) shown in Table 5:1 will be fully discussed in Chapter 8.

Chapter 6

Review: Levels of hypnotic drug prescribing and usage among the elderly

As the variety of drugs which modify behaviour has increased over the past 20 years, so too has epidemiological interest in the prescribing and use of these medications. Most of this attention has focussed on psychotropic drugs as a single operationally defined entity (variously including neuroleptics, tranquillizers, hypnotics, stimulants, and anti-depressants). This literature shows a consistent relationship between the use of psychotropic drugs, when these drugs are considered collectively, and age. Reports from the United Kingdom (e.g. Skegg et al. 1977), the United States (e.g. Parry et al. 1973), Canada (e.g. Fejer and Smart, 1973) and Sweden (e.g. Boethius and Westerholm, 1977) concur in that the prevalence of psychotropic drug usage tends to increase with age. Where surveys have examined the use of individual drug groups, however, it is evident that hypnotics are principally responsible for producing this particular age related trend. More so than for any other psychotropic drug, the prevalence of hypnotic drug usage has been shown consistently to increase with advancing age (Parish, 1971; Mellinger et al. 1971; Parry et al. 1973; Skegg et al. 1977; Murray et al. 1981).

In view of the higher incidence of adverse drug responses, and the increasing likelihood of drug usage with advancing age, the use of hypnotics among older age groups merits detailed

assessment. In this chapter information concerning hypnotic drug usage among the elderly is reviewed, and trends in usage are analyzed. The present review has two further aims. First, to assess the impact of relevant clinical reports and experimental studies on the pattern and prevalence of sedative-hypnotic drug usage among the elderly over the past 20 years. Secondly, to evaluate the causal status of some of the demographic variables associated with elderly hypnotic users.

Several drug-associated factors influence the probability of adverse behavioural reactions occurring in older hypnotic users. These include the pharmacological characteristics of the drug (e.g. long half-life/short half-life), the pattern of usage (intermittent/continuous; long term/short term), and the dosage employed. A thorough appraisal of the degree to which elderly individuals are exposed to the risks of hypnotic drug usage, therefore, requires information on four specific aspects of consumption: 1) the extent to which sedative-hypnotic drugs are used by the elderly; 2) the duration, and the continuity of usage; 3) the drug used; and 4) the dosage used. This review considers the epidemiological literature on hypnotic drug use among the elderly in relation to these four aspects of drug consumption.

Methodological considerations

To minimize the problem of between-study comparisons arising from differences in definitions, methodologies, and the demographic characteristics of samples, the criteria employed to

select studies have concentrated on prevalence rates of drug use. For the studies which met these criteria, a further distinction was made between surveys of institutionalized populations, and surveys of community samples. This distinction broadly recognizes the existence of differing clinical needs and environmental pressures which possibly mediate hypnotic drug use within these two elderly populations. The institutional settings included are: hospitals (general, psychiatric, geriatric and psychogeriatric); nursing homes (long or short stay); and residential homes for the elderly.

It was also necessary to draw a distinction between studies of prescribing, and studies of drug usage. Analyses of prescribing can utilize at least two sources of information, physician's records of prescriptions issued, or pharmacist's records of prescriptions dispensed. Both methods are likely to overestimate, to an unknown extent, drugs actually used. As Williams (1979) has pointed out, prescribed medicines are not necessarily dispensed, and dispensed medicines are not necessarily consumed. It is also the case, however, that studies of general practice prescribing do not take into account the minority of individuals who receive prescriptions from hospital outpatient departments.

Questionnaire surveys, where individuals report taking, or having taken, prescribed drugs may, on the other hand, underestimate actual drug usage. Parry et al. (1970), comparing interview and prescription data, report a tendency for some

respondents falsely to report not taking drugs. Irrespective of the merits or demerits of these two methodological approaches, the posible influence of these error sources is recognized in this review.

Method

Reports and surveys likely to include information on hypnotic drug prescribing and/or usage were identified through social science abstracting journals, Index Medicus, the Key Word in Context Index of Sleep Research, and through cross references from relevant articles. The present review includes prevalence rates from those studies which met the following criteria: 1) the study was published in an English language scientific or professional journal, or appeared in an accessible government report, between 1960 and 1981. 2) An elderly population or sub-population was implicitly (e.g. geriatric patients) or explicitly (e.g. categories of 70y+, or 65-75y, etc.) defined. In this review, "elderly" generally refers to those aged 65y and over; however, studies in which the oldest age group defined was 60y+ were considered acceptable. 3) Surveys of non-institutionalized populations observed appropriate sampling procedures which reduced the probability of over-including members of clinically defined sub-groups with known sleep disturbances (e.g. those with sleep associated respiratory impairment; the clinically depressed, etc.). 4) If the study examined the prescribing and/or use of more than one class of psychotropic drugs, data relating to sedative-hypnotic substances were unambiguously specified.

"Hypnotics", and "sedative-hypnotics" are defined here as drugs with sedative properties, the administration of which is intended to promote sleep. 5) The study provided either a prevalence rate, or prevalence rates, of sedative-hypnotic drug usage among the elderly, or presented numerical data from which such rates could be calculated.

Studies which did not satisfy all of the above criteria, but which did contain relevant information, are cited where appropriate. All studies are evaluated with reference to the four aspects of drug usage previously mentioned, viz. Prevalence of drug usage: Both point- and period-prevalence are considered.

Duration and frequency of usage: Duration refers to the minimum period that individuals within a particular sample have been taking, or receiving prescriptions for, sedative-hypnotic drugs. Frequency refers to the continuity of usage; in practice, where studies have referred to the frequency of usage, the reference is often descriptive rather than quantitative (e.g. "regularly", "sometimes", etc.).

Drugs used: Drugs are considered in terms of pharmacological categories (e.g. benzodiazepines; barbiturates, etc.), or specific hypnotic preparations.

Dosage employed: Dose refers to the mg weight, and not to the number of tablets or capsules, or to the volume of liquid medicines consumed.

Prevalence of Drug Usage

Studies which yielded prevalence rates of hypnotic drug prescribing and/or usage among the non-institutionalized and the institutionalized elderly are shown in Tables 6:1 and 6:2 respectively. Collectively, the 18 prevalence rates show wide inter-study variations, ranging from 5.9% (Wilks, 1975) to 54.0% (Mulligan and O'Grady, 1971). While these studies represent a variety of methodologies and designs, it would be over simplistic to conclude that the observed inter-study variations arose primarily from procedural differences. Studies which have employed standardized research methodologies have shown similarly wide variations in hypnotic drug prescribing and usage between countries (Balter et al. 1974), within a country (Parry et al. 1973), and between medical practices (Parish, 1971) and hospital units (Winstead et al. 1976) within cities. Thus, when methodologies are controlled, variations in prevalence continue to emerge, probably as a characteristic of the drug-use phenomenon itself, and not as a characteristic of the way that phenomenon is quantified.

Individual differences in prescribing behaviour may also contribute to inter-study variations in reported prevalence. Wilks (1975), for example, reports a one-year prevalence rate for the patients of a single practitioner, viz. 5.9%. The one-year prevalence rate for the age group 60y+ reported by Skegg et al. (1977), 21.6%, represents the combined prescribing of 19

Table 6:1 Studies reporting prevalence rates of hypnotic drug prescribing/ usage among the non-institutionalized elderly

Study	Origin	Age of Sample	Sample size	Prevalence Rates (%) male	female	total
McGhie and Russell (1962)	UK	75y+	-	25.0	45.0	-
Manheimer et al (1968)	USA	60y+	228	10.0	13.0	11.2
Mellinger et al (1971)	USA	60y+	296	9.0	13.0	11.5
Stevenson and Gaskell (1971)	UK	70y+	185	-	-	14.6
Dunnell and Cartwright (1972)	UK	65y+	281	-	-	18.1
Parry et al (1973)	USA	60y+	550	7.0	8.0	7.6
Gruer (1975)	UK	65y+	762	-	-	19.0
Wilks (1975)	UK	65y+	256	6.4	5.5	5.9
Law and Chalmers (1976)	UK	75y+	151	-	-	8.6
Karacan et al (1976)	USA	70y+	-	12.3	22.0	18.3
Skegg et al (1977)	UK	75y+	1360	21.4	29.9	27.3
Gerrard et al (1978)	UK	65y+	103	18.0	40.0	33.0
Williamson and Chopin (1980)	UK	-	1998	22.6	22.0	22.2
Murray et al (1981)	UK	65y+	1137	6.1	12.0	9.7

- information not provided

Table 6:2

Studies reporting prevalence rates of hypnotic drug prescribing/usage among the institutionalized elderly

Study	Type of institution	Age of population	Size of population	Prevalence rates (%) male	female	total
Mulligan and O'Grady (1971)	psychogeriatric units	-	189	-	-	54.0
Ingman et al (1975)	extended nursing care facility	-	131	-	-	22.9
Christopher et al (1978)	general and psychiatric hospital units	65y+	873	-	-	51.8
Saltzman and Van der Kolk (1980)	general hospital	60y+	195	-	-	22.6

- information not reported

practitioners in five group practices. Both studies were conducted in England, and both used prescription records as a primary source of information. These differences also serve to illustrate a further and, in terms of reported prevalence, influential feature of some prescribing surveys. Many surveys of general practice prescribing are conducted by physicians who analyze their own prescribing behaviour. Williams (1979) has suggested that practitioners interested in such research are possibly atypically low prescribers. In this respect, it is relevant to note that, of the three studies reporting the lowest prevalence rates shown in Table 6:1, two of these (Wilks, 1975; and Law and Chambers, 1976) were conducted by general practitioners within their own practices.

Differences in the characteristics of survey samples present a further source of inter-study variability in reported prevalence rates. Two characteristics in particular appear to exert a systematic influence on the total levels of hypnotic drug usage shown in Tables 6:1 and 6:2, namely, the age structure, and the institutionalized/non-institutionalized status of samples. These two factors will be considered in turn.

Many of the studies included in this review report data only for open-ended age categories (e.g. 60y+, 65y+, etc.). Those studies which provided a more detailed analysis of their elderly samples, however, show a continuing age related increase in hypnotic drug usage, from 65y+ to 75y+ (McGhie and Russell, 1962), from 60-69y, through 70-79y, to 80-89y (Stevenson and Gaskill,

1971), from 60-69y to 70y+ (Karacan et al. 1976), and from 60-74y to 75y+ (Skegg et al. 1977). It can be seen from Table 6:1 that most of the total prevalence rates are derived from samples having four minimum age levels viz, 60y, 65y, 70y, and 75y. The average total prevalence reported for each of these four minimum age levels is shown in Table 6:3. This rather simplistic analysis does indicate that rates of hypnotic prescribing and/or usage tend to increase with the minimum age of the elderly sample studied. This influence of sample age structure on reported levels of drug prescribing/usage is also relevant when comparing the US and UK studies shown in Table 6:1. Although sedative-hypnotic drug usage appears (from Table 6:1) to be lower in the United States, three out of the four US total prevalence rates are for the age group 60y+ (i.e. Manheimer et al. 1968; Mellinger et al. 1971; Parry et al. 1973) and probably underestimate usage in older age groups. This conclusion is supported by the study of Karacan et al. (1976) which reports a considerably higher prevalence rate for American adults aged 70y+.

Table 6:3. Total prevalence rates from Table 6:1 averaged according to the minimum age of the sample

minimum age of sample	average prevalence of hypnotic drug usage
60y+	10.1%
65y+	17.1%
70y+	16.5%
75y+	18.0%

Comparing the prevalence rates reported for institutionalized populations and community samples, it is clear that the higher levels of sedative-hypnotic drug usage are found among elderly hospital patients. The evidence also suggests that levels of usage are highest in those hospital units which specialize in the care of the elderly, i.e. geriatric and psychogeriatric units. Mulligan and O'Grady (1971) report a prevalence rate of 54% for psychogeriatric patients, and Christopher et al. (1978) found that patients in geriatric units were more likely to receive sedative-hypnotic drugs than were elderly medical, surgical, psychiatric, or mentally subnormal patients. Salzman and Van der Kolk (1980), on the other hand, report relatively lower levels of usage for elderly general hospital patients (22.6%), a rate similar to that

reported by Ingman et al. (1975) for nursing home residents, and by Bruce (1982) for a small residential home. Thus, it appears that high levels of physical dependency in the elderly are associated with high levels of hypnotic drug usage.

Temporal trends. Methodological differences which obstruct direct inter-study comparisons also prevent detailed conclusions being drawn regarding temporal trends in usage. One conclusion that is possible, however, is that in the 20 years covered by Tables 6:1 and 6:2, the elderly have remained a popular target group for sedative-hypnotic substances. Considering only the community-based samples in Table 6:1, it can be seen that, more often than not, the rate of hypnotic drug usage among the elderly is reported to approach, or to exceed 10%. Viewed as estimates (in many cases, very crude estimates) of usage in the general population, these rates must be interpreted against the background of change in both the size, and the structure, of the elderly population over the past 20 years. The absolute number of individuals aged 65y+ rose by 8.1 million between 1960-1979 in the United States, and by 1.7 million between 1962-1977 in the United Kingdom (United Nations, 1964; 1980). Similar percentage estimates of hypnotic drug usage reported periodically between these dates therefore, represent in absolute terms, increasing number of elderly individuals. Thus, assuming a conservative prevalence estimate of 10%, the number of elderly individuals consuming hypnotic drugs in the United Kingdom has risen from 0.6 million in 1962, to 0.8 million in 1977. The proportion of elderly individuals aged 80y+ has also increased during the period

covered by this review. The very elderly, i.e. those 80y and over, constitute approximately 20.7% of the elderly population in the United States, and 17.2% in the United Kingdom (1979 and 1977 census data respectively). Given, then, that in some studies the prevalence of hypnotic drug usage reported continues to increase until well after the 65th year of age, then these rates, too, are progressively representing an ever increasing number of very elderly individuals.

The pattern of usage also shows some consistency over time. McGhie and Russell (1962), Dunnell and Cartwright (1972), and Murray et al. (1981) all report that levels of hypnotic drug usage increased progressively with age from early adulthood onward. Whatever clinical or psycho-social circumstances mediate the use of sedative-hypnotic drugs across all age groups, the bias towards the elderly arising from these circumstances has remained largely unchanged for almost 20 years.

Sex-differences in usage. The most consistently reported demographic feature of the surveys shown in Table 6:1 is the presence of sex diferences in usage. Irrespective of when or where the study was conducted, whether prescribing or usage was analysed, or how hypnotic drugs were defined, the use of sleeping drugs is generally reported to be higher among elderly females than among elderly males. [The clinical importance of this finding is emphasized by the data of Salem et al. (1982) which suggests that elderly females may be more profoundly affected by some hypnotics; see previous chapter]. Only two exceptions to

this trend are shown in Table 6:1, Wilks (1975), and Williamson and Chopin (1980). The study by Wilks (1975) is clearly uncharacteristic in other respects, for example, the single-practitioner methodology, and the extremely low total prevalence reported. It is not unreasonable to conclude, therefore, that the higher usage of hypnotics found among male patients in this study reflects, to some extent, the atypical prescribing practices of a single practitioner. The results of Williamson and Chopin (1980) are derived from prescription analyses of patients consecutively admitted to 49 geriatric centres in England and Wales. The slightly higher usage of hypnotics by males found by these researchers will be discussed later in this review.

Sex differences in the use of prescription sedative-hypnotic drugs are less clearly defined among the young than they are among the middle-aged or elderly. Manheimer et al. (1968), Mellinger et al. (1971), Karacan et al. (1976), and Murray et al. (1981) all report very similar levels of usage for males and females in the age group <30y. Usage is generally shown to increase with age for both sexes, but in most analyses of age-stratified samples, this increase has been shown to be more profound for females (McGhie and Russel, 1962; Manheimer et al. 1968; Melinger et al. 1971; Parry et al. 1973; Murray et al. 1981). McGhie and Russell (1962), for example, comment that "... the habit of taking a hypnotic increases for both sexes with advancing years, but that both the incidence and its acceleration with age are more pronounced in the case of women." Similarly, Murray et al. (1981) observed that "The proportion of drug consumers taking an hypnotic

increased with age (particularly for women)." Clearly, then, both sex and age combine to influence the usage of hypnotic drugs in later life. In order, therefore, adequately to account for sex differences in usage among older adults, the interacting factor of age must be taken into consideration.

It is interesting to note that these consistently reported sex-differences in the use of sleeping drugs do not appear to be mediated by similarly consistent differences in the objectively measured (electroencephphalographic) sleep patterns of elderly males and females. While Williams et al. (1974) report superior sleep efficiency in elderly females relative to elderly males, the studies of Kahn and Fisher (1969) and Kahn et al. (1970) suggest that elderly males sleep better than elderly females. In a more recent study, Hayashi and Endo (1982) found no significant differences between the electroencephalographically recorded sleep of five males (mean age = 79y) and ten females (mean age = 83.5y) on measures of total sleep time, total sleep stages 1 and 2 (drowsiness and light sleep), total sleep stages 3 and 4, or total rapid eye movement (REM) sleep.

Few of the studies shown in Table 6:1 attempted to account for sex differences in drug usage, and, of those that did, none addressed the interacting influences of ageing and sex on sedative-hypnotic drug consumption. Furthermore, attempts to account for gender differences in usage tended to encompass, not only all age groups, but also all psychotropic drugs. Such broadly based

explanations do not differentiate the clinical and therepeutic needs which mediate the use of hypnotics from those which mediate the use of other psychotropics, and therefore can only partially explain the age/sex pattern so characteristic of hypnotic drug usage. Parry et al. (1973), for example, list sociological, psychological, and physiological factors which might lead to higher rates of prescription psychotropic drug usage among adult females. Also, both Mellinger et al. (1971) and Parry et al. (1973) suggest that males are more likely to use "alternative coping drugs" like alcohol and marihuana. With particular regard to older women, the possible influence of menopause and bereavement on tranquillizer, sedative, and hypnotic usage was further recognized by Parry et al. (1973). In the absence of data collected specifically to test these hypotheses, whether, and to what extent these factors influence the pattern of hypnotic drug usage among the elderly, remains a matter for speculation. From the available literature it is, nevertheless, possible to identify demographic variables which might plausibly contribute to higher levels of hypnotic drug consumption among older females.

Associations between bereavement and hypnotic drug usage are noted in several studies. Manheimer et al. (1968), not distinguishing between the sexes, report that the highest level of sedative-hypnotic drug use was among widows/widowers. More specifically, Stevenson and Gaskell (1971) report that 37% of their female hypnotic users were widowed, compared with only 8% of males in the same survey. In an earlier study of 97 users of repeat prescriptions for hypnotic drugs, Johnson and Clift (1968)

found that the proportion of widows (35%), but not widowers, was significantly higher than that found in the general population. These associations between the use of sleeping tablets and bereavement may be interpreted at two different levels. Parry et al. (1973), for example, emphasize the immediate emotional stress of bereavement, and suggest that the prescribing of sedatives and hypnotics for women during mourning is "commonplace". This suggestion is consistent with the sociological model of prescribing presented by Cooperstock (1971) which argues that (predominantly male) prescribers expect female patients to be more emotionally reactive, and more in need of psychotropic drugs. Not all elderly widows, however, are in mourning, and those that are probably represent only a minority of bereaved women. Among those women who have been widowed for some years, it is likely that marital status, as a predictor variable, has been confounded with other age-dependent variables, particularly health status. Statistically, women tend to live longer than men, and are therefore more exposed to the debilitating consequences of advanced age. Thus, it is possible that increasing age among females is associated, not only with an increased probability of widowhood, but also with reduced physical health status relative to males.

The relationship between physical health status and hypnotic drug usage in the elderly has not been thoroughly investigated. Both Cooperstock (1971) and Murray et al.(1981) suggest that sex differences in psychotropic drug usage as a whole are independent of health status. Using global self-assessments of health, and

the General Health Questionnaire, Murray et al. (1981) demonstrated that, when age and health status are controlled, sex differences in consumption persist. However, such analyses do not consider the use of hypnotic drugs alone, nor the more frequent use of hypnotics in the treatment of physical, as opposed to psychiatric, illnesses. Stevenson and Gaskell (1971), for example, report that almost 40% of their adult patients receiving repeat prescriptions for hypnotic drugs commenced taking these drugs for essentially somatic disorders. The divergent patterns of sedative-hypnotic drug usage between ageing males and ageing females are also ignored when psychotropic drugs are grouped as a single therapeutic entity. Indeed, as the data of Murray et al. (1981) show, when psychotropic drugs are considered collectively, the effects of ageing are the same for both sexes, which is certainly not the case when hypnotics are considered alone. Consequently, the findings of this, and other similar analyses, do not rule out the possibility that some of the variance in hypnotic drug usage between ageing males and ageing females may be accounted for in terms of further sex differencesin physical health status.

That a relationship does, in fact, exist between physical health and sleeping drug usage is strongly inferred by demographic data collected by the American Cancer Society in 1959-60, and by subsequent six-year follow-up interviews. This extensive survey of over 800,000 individuals showed that mortality among respondents who reported using sleeping tablets "often" was twice that of age matched controls who reported no sleeping tablet use

(Kripke et al. 1979). This is not to suggest that sleeping tablets are causally implicated in the higher mortality rates, but rather that the need for drug-induced sleep, and the associated higher mortality risk, have a common cause, possibly lower physical health status.

The hypothesis that health status differences between ageing males and females may influence the observed sex difference in hypnotic drug usage within this age group necessarily predicts that, when health status variables are controlled in the analysis of an elderly population, sex differences in hypnotic drug use will, at least, be attenuated. If we can assume that physical health status is much less variable among elderly hospital admissions than itis among the elderly at large in the community, then the study of Williamson and Chopin (1981) provides hypnotic drug-use data for an aged population in which the severity of physical illness has, to some extent, been controlled. These authors analyzed the prescription medications of 1998 consecutive admissions to geriatric units and, as can be seen from Table 6:1, the proportions of males and females receiving sedative-hypnotic drugs is almost identical. Also, as would be expected if physical health status is related to hypnotic drug usage, the total prevalence rate is relatively high when compared with other United Kingdom surveys. It is also interesting to note that, of the 1321 females, and 677 males included in this survey, proportionately more females were aged over 75y.

On the same grounds, a similar 'ironing out' of sex differences might be predicted for residential institutions. Unfortunately, the only relevant study shown in Table 6:2 (Ingman et al. 1975), does not provide separate drug-use information for both sexes.

Finally, the possibility that males employ substitutes for prescription hypnotic drugs does find some support in the current drug use literature. Both Mellinger et al. (1971), and Parry et al. (1973) report that, when non-prescription drugs (particularly the so called "over-the-counter hypnotics") are taken into consideration, sex differences in total drug usage are diminished. The data of Mellinger (1971) indicates that males and females over 60y are equally likely to report the use of non-prescription "psychotherapeutic" compounds. A study of insomniacs in Los Angeles conducted by Guilleminault et al. (1977) directly linked the use of alcohol among males with hypnotic drug substitution. These researchers found that significantly more males made frequent use of alcohol as a remedy for poor sleep. However, age related trends in this practice were not investigated.

Sex differences in the <u>pattern</u> of hypnotic drug usage among the elderly are also evident from the studies reviewed here. These differences are more relevantly discussed in the next section.

Duration and Frequency of Usage

Information on the duration and/or frequency of sedative-hypnotic drug usage among the elderly was provided in only a minority of the studies shown in Tables 6:1 and 6:2. All the surveys of institutionalized populations yielded point-prevalence data, as did the study by Williamson and Chopin (1980). These surveys report only the prevalence of drug usage at a particular point in time, without reference to antecedent patterns of usage. Of the community based surveys, those of Dunnell and Cartwright (1972) and Murray et al. (1981) provide two week prevalence rates, and that of Skegg et al. (1977) provides a one year prevalence rate. These period prevalence studies report the proportion of individuals taking, or receiving prescriptions for, hypnotic drugs at any time within the period specified. None of these studies distinguished between regular or irregular, frequent or infrequent usage.

In the remaining studies, the research methodology allowed for a minumum duration and/or frequency of usage to be assessed. This was done either directly, by including more than one response category relating to the use of hypnotic drugs in a survey questionnaire (e.g. used sometimes, often, always, etc.), or indirectly, where the use of repeat prescriptions implied regular consumption. Table 6:4 shows the total prevalence rates reported in relation to the duration and frequency of usage derived from these studies. Excluded from this table are the studies of Melinger et al. (1971) and Parry et al. (1973). While both of

TABLE 6:4

Studies reporting frequency and/or duration of hypnotic drug prescribing/usage among the elderly

	prevalence rates (%)		
	used 'regularly'	used 'occasionally'	minimum duration of usage
McGhie and Russell (1962)	25.0 (M) 45.0 (F)	- -	- -
Manheimer et al (1968)	11.2	-	-
Stevenson and Gaskell (1971)	14.6	-	1 year
Gruer (1975)	19.0	-	-
Wilks (1975)	5.9	-	3.5% > 1 year 2.3% < 1 year
Law and Chalmers (1976)	8.6	-	-
Karacan et al (1976)	8.2 (M) 4.9 (F)	4.1 (M) 17.1 (F)	- -
Gerrard et al (1978)	15.0 (M) 31.0 (F)	3.0 (M) 9.0 (F)	

- information not reported

these studies provided information on duration and frequency of psychotropic drug use, in neither case did these data relate specifically to hypnotics and the elderly.

As can be seen from Table 6:4, many of the total prevalence rates already discussed are rates of frequent usage. Two exceptions to this, Karacan et al. (1976) and Gerrard et al. (1978), show differing trends in usage. In an urban county of Florida, USA, Karacan et al. (1976) found that hypnotic drug use among elderly females was more likely to be reported as occasional, whereas among elderly males it was more likely to be reported as "often or all the time". On the other hand, Gerrard et al. (1978) found less occasional usage among their elderly sample in London, with both males and females more likely to report taking hypnotics "every night". While this discrepancy between the two surveys might be attributable to the respondent's interpretation of different questions, it is also possible that these results indicate a real difference in the pattern of usage between the two communities. In this respect it is relevant to note that the surveys of Melinger et al. (1971), and Parry et al. (1973), both of which were conducted in the United States, show that, among psychotropic drug users, males are more likely to report regular use, over long periods of time, than are females.

Only two studies provided numerical information on durations of hypnotic drug usage. Stevenson and Gaskell (1971), using clinical records, found that among their sample of hypnotic drug users the minimum duration of usage was one year. It is also

interesting to note that, in follow-up interviews, these authors further observed that "Elderly patients, in particular, were....more likely to underestimate the length of time they had been taking hypnotics". This comment emphasizes the need for caution in interpreting questionnaire data on certain aspects of drug use among the elderly. Wilks (1975) examined the duration of hypnotic drug usage in some detail, and reports that of ten patients who had received hypnotics for more than one year, nine were aged over 65y, and five of these were aged over 80y. Further evidence that the elderly are likely to continue taking sedative-hypnotic drugs for long periods of time (i.e. more than one year) is provided by the longitudinal studies of Boethius and Westerholm (1976; 1977). These authors analyzed the prescription records of 2,566 individuals in a single county of Sweden. Substantial proportions of elderly outpatients who, in 1970, were categorized as regular, intermediate, or occasional users of "hypnotics, sedatives, and/or tranquillizers" continued to purchase these drugs up to five years later.

Drugs and Dosages Used

Several of the studies shown in Tables 6:1 and 6:2 provide information on specific drugs, or drug groups, used as hypnotics by adults of all ages. Only a few surveys report these data for elderly samples, and few of these report any dosage information. During the period covered by this review (1962-1981) the prescribing of barbiturate psychotropic drugs declined in popularity, and non-barbiturate preparations, particularly

benzodiazepines, showed a reciprocal increase in usage. This historical trend, well documented by Parish (1971) and Howie (1975) in the United Kingdom, and by Cooper (1977) in the United States, is clearly reflected in the hypnotic drug-use data considered in this section. In the studies conducted by Manheimer et al. (1968), Mellinger et al. (1971), and Parry et al. (1973), the questionnaire definitions of hypnotics are exemplified mainly by barbiturate drugs, the principal exception in all three cases being glutethimide. Stevenson and Gaskell (1971) report that almost 80% of their hypnotic prescriptions (for all age groups) were for barbiturate drugs, particularly amylobarbitone. Wilks (1975), on the other hand, reports the use of barbiturates in only 41% of hypnotic users, the remaining 59% receiving nitrazepam or methaqualone (as Mandrax). The increasing use of nitrazepam in Europe is also illustrated by the data of Boethius and Westerholm (1976). This single drug was found to represent 28% of sedative-hypnotic purchases in 1970, and 55% in 1975.

As regards the elderly, most of the detailed analyses of drugs prescribed are provided by the surveys of institutionalized populations. Of 102 psychogeriatric patients receiving hypnotics, Mulligan and O'Grady (1971) found that 70% received methaqualone (as Mandrax), 17% dichloralphenazone, 7% chlormethiazole, and 7% nitrazepam or barbiturates. No dosages are reported. Several years later, a very different pattern of drug use among elderly hospital inpatients was reported by Christopher et al. (1978). These researchers note that, of 452 elderly patients prescribed hypnotic drugs, 62% of prescriptions

were for chloral derivatives, 21% were for nitrazepam, and 17% were for other non-barbiturate hypnotics. Contrasting these two hospital surveys, both nitrazepam and chloral derivatives (e.g. dichloralphenazone) appear to have increased in popularity as hypnotics for the elderly. For nitrazepam, this increase in popularity seems to be general to all age groups (at least in Europe). Compare, for example, the results of the general practice survey conducted by Stevenson and Gaskell (1971), in which only 3.8% of patients were found to receive nitrazepam, with that of Skegg et al. (1977) which reports that nitrazepam was one of the most commonly prescribed of all drugs. In contrast, the use of chloral derivatives among elderly hospital patients may reflect the preferential use of these drugs in this age group. Support for this possibility is provided in a survey of medications received by nursing home residents in the US, and reported by Ray et al. (1980). These researchers comment on the extensive use of chloral/benzodiazepine combinations as hypnotics among nursing home residents in Tennessee, USA.

General practice analyses of hypnotic drug prescribing among patients of all ages tend to show a consistent low-level of prescriptions for chloral derivatives. Stevenson and Gaskell (1971), and Wilks (1975) report that Trichloryl and/or chloral represented 2.6% and 3.4% respectively of total hypnotic prescribing. Similarly, of the 1,145 hypnotic prescriptions analyzed by Parish (1971), 4% were for chloral derivatives. If these low levels of prescribing are due to selective use among the elderly, then higher rates of usage,

possibly approximating those of the hospital surveys, would be expected if the elderly were considered alone. The conclusion that dichloralphenazone is used preferentially among the elderly is certainly consistent with the drugs reputation as a "...safe and satisfactory hypnotic of first choice" for the elderly patient (Evans and Jarvis, 1972). It is cautionary to note, however, that long-term chloral hydrate use has been associated with confusion and hallucinations in dependent geriatric patients (Kramer, 1967).

The increasing use of benzodiazepine sedative-hypnotic drugs among the elderly is also shown in the more recent North American surveys. An extensive report on the risks and benefits of sedative-hypnotic drugs compiled by the National Institute on Drug Abuse, and edited by Cooper (1977), shows that the hypnotic most extensively prescribed by general practitioners in the United States is flurazepam. The preferential use of this benzodiazepine among the institutionalized elderly in the United States is clearly shown in two further studies. Saltzman and Van der Kolk's (1980) survey of 192 general medical inpatients over the age of 60y shows that, of the 44 patients prescribed hypnotics, 39 received flurazepam, 3 chloral hydrate, and 2 received barbiturates. Marttila et al. (1977), in a study of 750 elderly patients in intermediate care facilities, report that 26% of these patients regularly received flurazepam.

Despite the overall paucity of information concerning hypnotic drug dosages typically prescribed for elderly patients, two of the more recent hospital surveys report dosage

distributions for nitrazepam and flurazepam respectively. Christopher et al. (1978) found that, among the 96 patients prescribed nitrazepam, 54 were prescribed 5mg, and 42 10mg. Of the 39 patients receiving flurazepam in Saltzman and Van der Kolk's (1980) survey, 15 received a 15mg dose, and 24 a 30mg dose.

Conclusions. Since the early study by McGhie and Russell (1962) the overall pattern of sedative-hypnotic drug use shows several consistent features. Prescription hypnotic drug usage continues to show an age-related increase; in the community this increase continues to be greater for females than for males. Also, for the elderly, institutional care appears to be consistently associated with a higher probability of receiving hypnotic drugs. Clearly, then, prescribing hypnotics has become firmly established as the intervention of choice in response to sleep complaints in the elderly.

While the epidemiological pattern of usage shows remarkably consistent features over time, the pattern of drugs actually prescribed has shown considerable changes. Among the adult general population, prescriptions for barbiturate hypnotics declined with increasing awareness of their toxicity and abuse potential, and the concomitant introduction of non-barbiturate sedative-hypnotic products. This transition is clearly reflected in the data relating specifically to the elderly. For very similar reasons, the rapid increase in the popularity of methaqualone (as Mandrax) was followed by an equally rapid

decline, a trend similarly reflected in the data derived exclusively from elderly populations. On the one hand, these trends suggest that hypnotic prescribing habits can change fairly uniformly as new information becomes available, and as viable alternative products are developed. On the other hand, it is not apparent that drugs of choice for the treatment of sleep disorders differ greatly between the old and the younger, despite the differential sensitivity to these drugs reported for different age groups.

From the more recent surveys, the extensive use of benzodiazepine hypnotics, particularly nitrazepam and flurazepam, also appears to be common to all age groups. Thus, with the exception of chloral derivatives for elderly inpatients, the information reviewed here provides no basis for concluding that the advanced age of the patient significantly influences the choice of hypnotic drug prescribed. Furthermore, from the scant data available, it is also impossible to conclude that caution in the prescribing of hypnotic drugs for the elderly is generally exercised at the level of dosage. While over half the nitrazepam users in Christopher et al.'s (1978) survey received a "low" (5mg) dose, 44% were prescribed 10mg. As Christopher et al. (1978) point out "While a dose of up to 10mg (of nitrazepam) is common for younger patients the official data sheet recommends up to 5mg per day for elderly patients." Saltzman and Van der Kolk (1980) show that well over one half of their small sample of flurazepam users received a 30mg dose. At this dosage flurazepam has been consistently associated with excessive CNS depression in elderly

patients (Greenblatt, Allen and Shader, 1977).

Currently available benzodiazepine sedative-hypnotic preparations differ widely in their duration of action, i.e. their elimination half-lives. Both nitrazepam and flurazepam are long acting, with reported half-lives within the range 21-28 hours (Breimer et al. 1977) and 47-100 hours (Kaplan et al. 1973) respectively. A problem associated with such long acting compounds is accumulation, either of the drug itself or of its active metabolites, with repeated use. The behavioural consequences of accumulation have been demonstrated by Oswald et al. (1979) for flurazepam. Over a 16 day period of nightly flurazepam (30mg) consumption, middle-aged volunteers became progessively more impaired on a variety of performance tasks. Where long half-life hypnotics are concerned, then, the frequency and duration of usage are of particular importance. Table 6:4, however, shows that the protracted use of sleeping tablets among the elderly is certainly not uncommon, supporting the suggestion that "...despite good intentions to the contrary, hypnotics are often prescribed for years rather than for short courses of treatment" (British Medical Journal, 1980).

From the more recent surveys, there is no evidence that short-life hypnotics are used either preferentially, or extensively, among the elderly.

Studies of hypnotic and psychotropic drug use are conducted for a variety of reasons, each study employing a design and

methodology suited to its particular objectives. These differences in approach produce differences in the detail and emphasis of reported data. Consequently, in this review it has been necessary to infer trends from information which is fragmented, and often lacking in detail. If we assume that the more recent surveys are representative of current hypnotic prescribing practices, then there is little to indicate a systematic attempt on the part of the prescribers to mitigate adverse behavioural reactions in elderly users. It should be remembered, however, that much of the information concerning specific drugs and dosages is derived from hospital-based surveys, and may, therefore, not be representative of the bulk of prescriptions which emanate from general practice. Caution is also necessary in evaluating the demographic data reviewed here. From the studies which report some hypnotic user characteristics, relationships are inferred between sex, marital and health status, and the use of hypnotic drugs. Again, in the absence of data which specifically elucidate these relationships, the role of these factors in determining hypnotic drug usage among the elderly remains obscure.

The assessment of behavioural risk within an elderly hypnotic drug-using population requires detailed information, not only on the specific drug types used, but also on the age structure of that population, the health status of drug users, the specific drug dosages employed, and the frequency and duration of usage. These, however, are among the most frequently omitted items of data in surveys of psychotropic or hypnotic drug usage. The present

review, therefore, emphasizes both the need for, and the information required of, clinically and psychologically relevant studies of hypnotic drug usage among the elderly.

Chapter 7

Two surveys of hypnotic drug usage, and factors influencing hypnotic drug usage in the elderly.

Introduction

From the current epidemiological literature it is evident that the use of prescription medications increases with the age of the patient (e.g. Knox, 1980). Adverse reactions arising from multiple prescribing for older patients have also recently been emphasized (Petersen and Thomas, 1975; Caird, 1977; Moir et al. 1979; Petersen et al. (1979); Knox, 1980; Williamson and Chopin, 1980; Raffoul et al. 1981; Bliss, 1981). Several surveys have further shown that hypnotics in particular are among the most frequently prescribed drugs for this age group (Christopher et al. 1978; Williamson and Chopin, 1980). The evidence reviewed in Chapter 5 indicates that, to an unknown extent, some elderly individuals are at risk from the use of some hypnotic drugs; certain characteristics of both drug and recipient may interact to increase the likelihood of adverse behavioural reactions occurring. Surveys of hypnotic drug usage, therefore, provide a means for estimating the degree of risk within an elderly drug-using population. Appropriately designed surveys of hypnotic drug use among the elderly can also serve to focus experimental attention on the most widely used drugs and dosages.

From the previous chapter, however, it is also clear that most surveys of sedative-hypnotic drug use among the elderly (or surveys which have included such information) place little

emphasis on the actual drugs, or the dosages, typically prescribed or used. As also pointed out, some hypnotics (e.g. long-acting cumulative compounds) are more likely to be associated with behavioural deficits in the elderly, and that the severity of such effects appear to be dose dependent. Thus, prevalence rates of hypnotic drug usage per se do not accurately predict the degree of risk within elderly populations, and, as a consequence, their value as feedback is diminished. In the present chapter, two surveys of hypnotic drug use among the elderly are described and evaluated. These studies were designed and conducted in order to provide the type of information which, as shown in Chapter 6, is most frequently omitted from the epidemiological literature. In addition to prevalence rates, therefore, the present surveys aimed to provide: i) details of drugs and dosages prescribed for, and used by, the elderly; ii) demographic characteristics of elderly hypnotic drug users; iii) details of any additional centrally acting medication prescribed for hypnotic users; and iv) some indication of the typical duration and frequency of hypnotic drug usage among the elderly. It was a specific intention of these surveys to identify, for subsequent experimental evaluations (Chapters 8 and 9), the most widely used hypnotic products in this elderly population. In both the design of the present surveys, and the selection of the survey population, three methodological issues were recognized and taken into consideration.

1) Defining Hypnotic Drugs

Hypnotic drugs form a semantic, rather than a pharmacological,

category of therapeutics. Drugs used as hypnotics may include drugs which are not marketed exclusively (and, therefore, are not readily identified) as hypnotics. Oswald (1980), for example, points out that "drugs which are sold for the treatment of anxiety are drugs which can be used as hypnotics". Certain neuroleptic and antidepressant drugs, while used to treat a primary psychiatric condition, may also be selected to exploit their sedative-hypnotic properties (British Medical Journal, 1980). It is also clear from some of the surveys reviewed in Chapter 6 (e.g. Ray et al. 1980) that phenothiazine tranquillizers are not infrequently used as the sedative-hypnotic of choice for some institutionalized elderly individuals. To minimize possible ambiguities in the present surveys, hypnotic drugs were operationally defined.

2) Prescribing and Usage

As fully described in the previous chapter, surveys of drug prescribing may overestimate the prevalence of actual drug usage. For this reason, the surveys reported here aimed to provide information only on drugs actually consumed.

3) The Survey Popoulation

Much of the detailed information relating to hypnotic drug usage among the elderly is derived from hospital-based surveys, while the majority of prescriptions emanate from general practice (see Chapter 6). Knox (1980) commenting on drug use surveys among the elderly observes that "There appears to be undue readiness to extrapolate results from hospital-based studies (relating to

highly selected populations) and to apply these to the community in general". Care was taken in the present studies to select an elderly population in which primary health care was provided by general practice physicians. The pattern of drug usage reported here, therefore, particularly as regards the drugs used, can reasonably be assumed to reflect the prescribing trends of general practitioners.

Methods

Survey Population. The surveys included all local authority homes for the elderly in Lothian Region, Scotland. This accommodation is defined in, and provided under, Part 4 of the National Assistance Act (Scotland) 1948. Within the terms of this act, accommodation is provided for those who, for reasons of "age or infirmity", are considered to be at risk in the community. [Detailed analyses of the health status, age structure, and sex distribution of this population are described below]. At the time of both studies, Lothian Regional Council provided 1160 residential places for the elderly in 24 different homes. Homes varied in size from 15 to over 300 beds. While larger homes contained both male and female residents, several of the smaller homes (i.e. <30 beds) admitted only males, or only females. All residents were under the care of their own general practitioner.

Study Design. The survey questionnaire was designed in collaboration with Lothian Regional Social Work Department, and

piloted in selected homes before the main surveys. The proforma eventually used is reproduced in Appendix 4:1. A glossary of drugs showing product and non-proprietary drug names likely to be used as hypnotics was attached to each proforma. This glossary is reproduced in Appendix 4:2. The surveys employed a point-prevalence design, the data for each being collected on a single specified night.

Prior to the first survey, the purpose of the study, and the nature of the information required, was explained to the Head of each home. Survey proformas were issued approximately 1 week before the surveys, and completed on the same nights throughout the region. For each resident receiving a hypnotic on those nights (15 October 1980; and 31 March 1981) data were collected on the age and sex of the recipient, the drug and dose received, whether that drug was given on the previous night, and on concomitantly prescribed centrally acting medication. For the purposes of these studies hypnotics were defined as drugs with sedative properties the administration of which was intended to promote sleep.

Additional Information. Details of the number, age, and sex of residents not receiving hypnotics, and consequently not included on the survey returns, was provided by Lothian Regional Social Work Department.

Analysis of Data. Survey data and additional information were combined, and frequency distributions for the variables of

interest were derived. Chi-square analyses of association were performed where appropriate.

The results from Survey 1 and Survey 2 will be presented in turn. The combined results from both surveys will then be discussed in detail.

Results (Survey 1)

The total study population comprized 1154 residents (373 males and 781 females). 387 residents (33.5%) received hypnotics on the night of the survey, and on the preceding night. The age distribution of hypnotic users and non-users is shown in Table 7:1. A significantly greater proportion of those aged 80y+ received hypnotic drugs (chi-square = 13.9, df = 3, $p<0.01$). The proportions of male and female hypnotic users are shown in Table 7:2. No significant association was found between hypnotic drug usage/non-usage, and sex (chi-square = 2.52, df = 1, NS).

Each hypnotic was grouped into one of ten categories. Eight of these categories were of single drugs (e.g. nitrazepam), the remaining two categories contained compounds having pharmacological and/or therapeutic similarities, viz. antidepressants, and major and minor tranquillizers. The phenothiazines promazine, chlorpromazine, and thioridazine, and the benzodiazepines diazepam and chlordiazepoxide accounted for most of the drugs in this latter category. The frequency with which each category of drug was used is shown in Figure 7:1. Of

Table 7:1. Age distributions of hypnotic users and non-users: (Survey 1)

	Age (years)				
	0-69	70-79	80-89	90+	Totals
No. (%) users	37 (9.5)	111 (28.7)	199 (51.4)	40 (10.4)	387 (100.0)
No. (%) non-users	88 (11.5)	273 (35.6)	306 (39.9)	100 (13.0)	767 (100.0)

Chi-square = 13.9, df = 3, $p<0.01$

Table 7:2. Hypnotic usage by sex: (Survey 1)

	Males	Females	Totals
Users: No. (%)	137 (35.4)	387 (64.6)	387 (100.0)
Nonusers: No. (%)	236 (30.8)	531 (69.2)	767 (100.0)

Chi-square = 2.52, df = 1, NS

Table 7:3. Dosage distributions for the four most frequently used single drugs: (Survey 1)

	No. receiving higher dose	No. receiving lower dose
nitrazepam	(10mg) 87	(<10mg) 40
chlormethiazole*	(>0.5G) 43	(0.5G) 21
triazolam	(0.125mg) 13	(<0.125mg) 22
temazepam	(20mg) 16	(<20mg) 15

* edisylate or equivalent

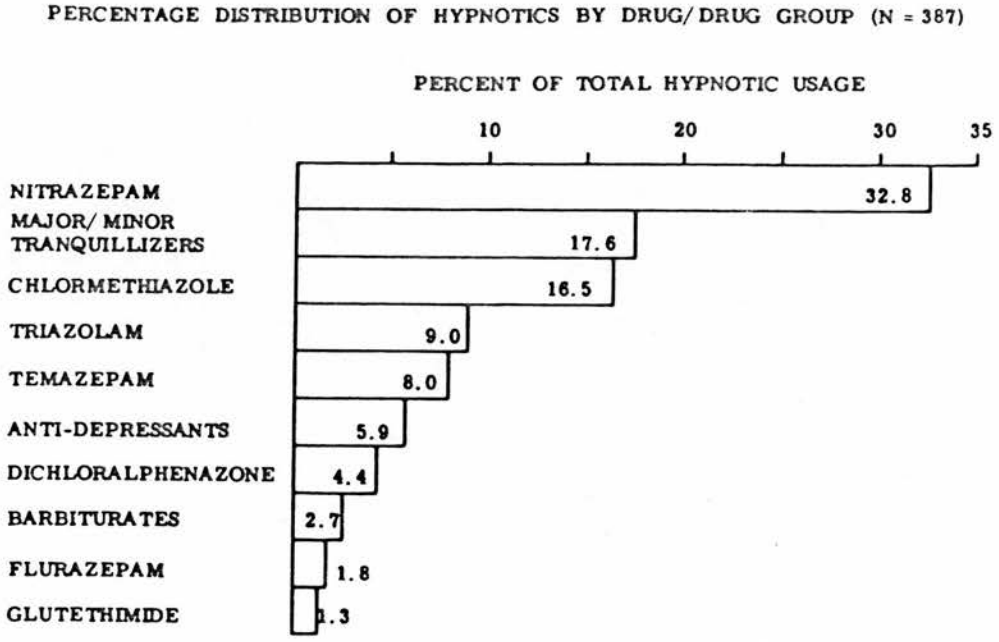


Figure 7:1 Distribution of hypnotic users by drug (Survey 1)

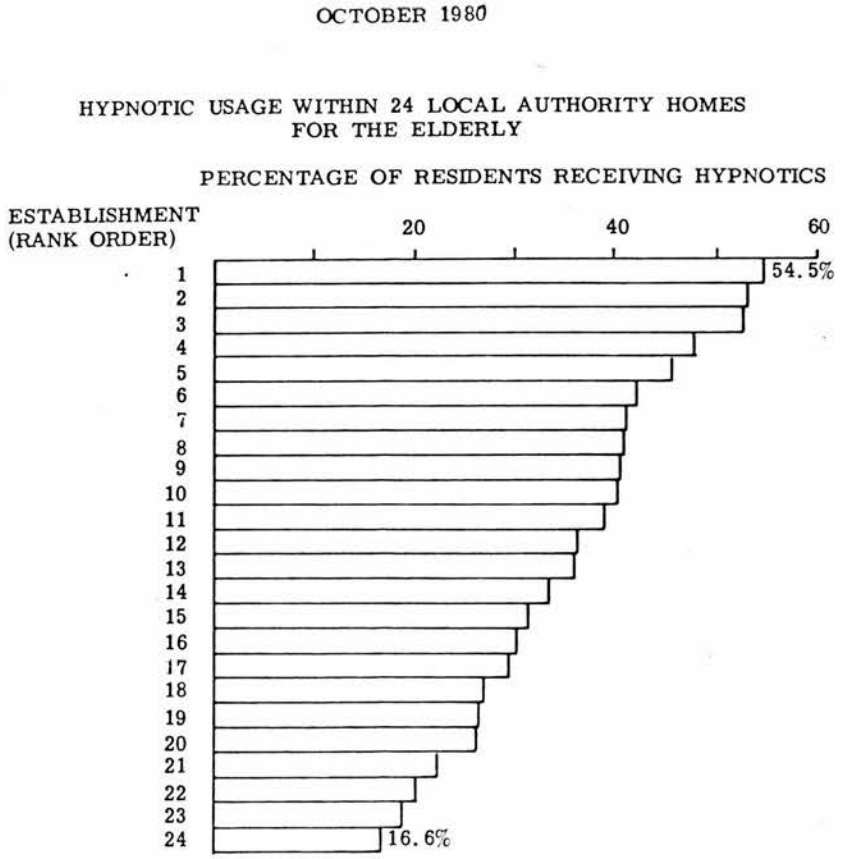


Figure 7:2 Distribution of hypnotic usage by home (Survey 1)

the four most frequently used single-drug hypnotics, nitrazepam was used by 127 individuals, chlormethiazole by 64, triazolam by 35, and temazepam by 31. Dosages for these four drugs, divided into "higher" and "lower" dose categories, are shown in Table 7:3.

For nitrazepam, chlormethiazole, and triazolam, these dosages were also analyzed in relation to the age of the recipient. No significant relationship was found between age and the dosage of nitrazepam (chi-square 2.05, df = 1, NS), chlormethiazole (chi-square = 4.06, df = 1, NS), or triazolam (chi-square [Yates' correction] = 3.44, df = 1, NS).

Of the 387 residents receiving hypnotics at the time of the survey, 163 (42.1%) were concomitantly receiving at least one centrally acting medication. These included major tranquillizers (62 cases), minor tranquillizers (20 cases), antidepressants (31 cases), and analgesics (31 cases). The remaining 19 cases comprized anticonvulsants, and antiparkinsonian treatment regimes.

The percentage of residents receiving hypnotics within each of the 24 establishments is shown in Figure 7:2. The prevalence of hypnotic drug use between homes showed wide variations, ranging from 16.6% to 54.5% (see Figure 7:2).

Comment

The prevalence of hypnotic usage found in this study, while

less than that reported for geriatric inpatients (Christopher et al. 1978), was greater than that reported for elderly individuals living in the community (Gerrard et al. 1978). In general, no preference was shown for the prescribing of short half-life hypnotics. It is likely, however, that in this age group, caution in the prescribing of hypnotic drugs is exercised at the level of dosage. Thus, Table 7:3 shows that, for the two most used single-drug hypnotics (nitrazepam and chlormethiazole), lower dosages were preferred.

It is interesting to note that, as predicted in Chapter 6, gender differences in usage are not prominent in this population. Table 7:2 shows no significant association between usage and sex. It is also relevant to note that the age diffences in usage shown in Table 7:1 accord with the earlier observation (Chapter 6; Table 6:3) that the use of hypnotic drugs continues to increase into the seventh or eighth decade of life.

Survey 2: Introduction

The second survey, conducted 24 weeks after the first, aimed to assess the consistency of the pattern and prevalence of drug usage reported above. A further interest of this second study, however, was the wide between-home variations in drug usage shown in Figure 7:2. In addition to age, sex, and drug-use information, this second survey included the simultaneous collection of data relating both to the social environment within each home, and to the general health status of individual residents. By examining

these data for factors associated with between-home variations in hypnotic drug consumption, it was hoped to identify possible determinants of drug usage at the level of the home, and at the level of the individual.

Methods

The survey was arranged to coincide with the 1981 Social Work Services Group (SWSG) census of residential accommodation. This national census requires each home to provide details of sex, date of birth, date of admission, and health status for each resident. For each individual resident, health status is also assessed using six dichotomous ratings (i.e. present/absent) of handicap and infirmity, viz. physical handicap; mental handicap; mental illness; chairbound or bedfast; regular incontinence; and mental confusion. The disabilities, or the degrees of disability, which merited a positive rating on each of these six indices of health status are shown in Table 7:4. These criteria for rating disability are derived from Social Work Services Group guidelines. A survey proforma, identical to that used in survey 1, was attached to, and completed with each SWSG census return.

Additional Information. Lothian Regional Social Work Department provided further data on: 1) the number of staff employed in each home; and 2) the number of General Practitioners attending each home.

Analysis of data. Drug survey, and SWSG census data were

Table 7:4. Scope of dichotomous handicap/infirmity ratings: summary of guidelines provided by the Social Work Services Group for the completion of SWSG census forms: (Survey 2)

Rating	Disability or Degrees of Disability
Physical Handicap	Blindness, Deafness, Severe Epilepsy, Limb Loss, Severe Arthritis, Cardio-vascular Disease, CNS diseases (stroke, multiple sclerosis, cerebral palsy).
Mental Handicap	Developmental delay such that the individual's mental performance is noticeably and consistently below that expected for any given chronological age.
Mental Illness	Diagnosed conditions under current treatment.
Mental Confusion	Residents whose confusion arises from brain pathology and is of a permanent irreversible nature.
Regular Incontinence	Daily incontinence of urine and/or faeces.
Chairbound/Bedfast	All immobile residents

combined, and frequency distributions of the variables of interest were derived. Chi-square analyses of association were computed where appropriate. Five measures relevant to the social environment within each home were also computed, viz. the percentage of male residents; the percentage of female residents; staff/resident ratio; general practitioner/resident ratio; and the total number of residents per home. Pearson product-moment correlation coefficients between each of these measures, and the level of hypnotic usage within each home were then computed.

Results

Analysis of Hypnotic Usage

All but one of the homes (rank 6, Figure 7:3) completed the survey proforma. The total survey population comprized 1122 residents. Of these, 382 residents (34.0%) received hypnotics both on the night of the survey, and on the previous night. The population parameters of the present (1981) and previous (1980) surveys are compared in Table 7:5. Figure 7:3 shows the distribution of hypnotic usage across homes. A Spearman rank order correlation was computed between these levels of usage, and those from the 1980 survey; a significant correlation obtained ($rho = 0.67$, $p<0.01$).

The age and sex distributions of hypnotic users and non-users are shown in Tables 7:6 and 7:7 respectively. No significant relationship was found between hypnotic usage/non-

Table 7:5. Comparison of populations from Survey 1 (1980) and Survey 2 (1981)

Survey	n	Females	Males	% Receiving Hypnotics	n of Homes
(1) 1980	1154	781	373	33.5	24
(2) 1981	1122	763	359	34.0	23

Table 7:6. Age distributions of hypnotic users and non-users: (Survey 2)

	Age (years)				
	0-69	70-79	80-89	90+	Totals
No. (%) users	31 (8.1)	117 (30.6)	185 (48.4)	49 (12.8)	382 (100.0)
No. (%) non-users	81 (10.9)	250 (33.8)	311 (42.0)	98 (13.2)	740 (100.0)

Chi-square = 5.1, df = 3, NS

Table 7:7. Hypnotic usage by sex: (Survey 2)

	Males	Females	Totals
Users: No. (%)	116 (30.4)	266 (69.6)	382 (100.0)
Nonusers: No. (%)	243 (32.8)	497 (67.2)	740 (100.0)

Chi-square = 0.6, df = 1, NS

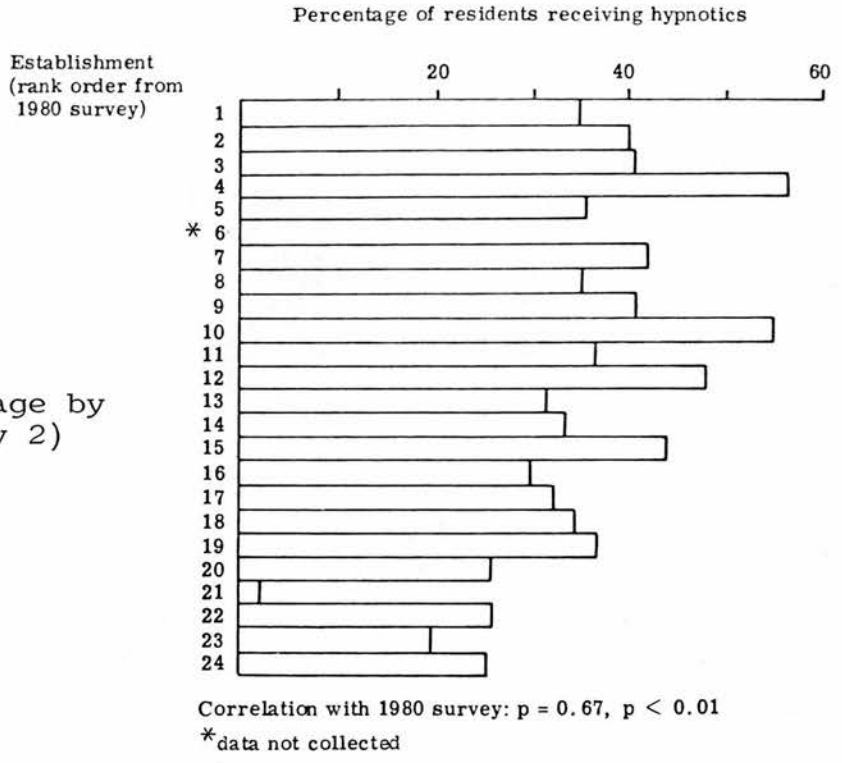


Figure 7:3
Hypnotic usage by home (Survey 2)

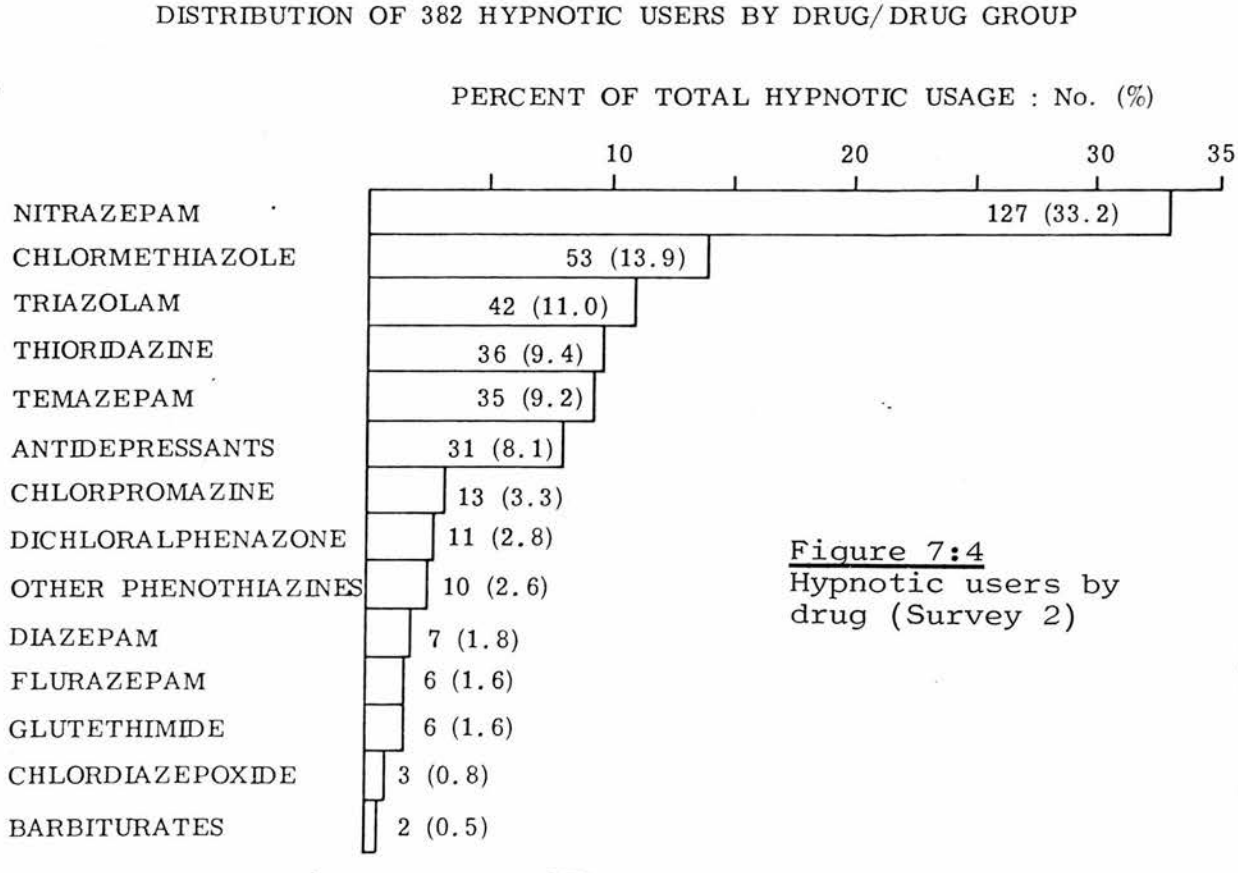


Figure 7:4
Hypnotic users by drug (Survey 2)

Table 7:8. Dosage distributions for the four most frequently used single drugs: (Survey 2)

	No. receiving higher dose	No. receiving lower dose
nitrazepam	(10mg) 35	(<10mg) 92
chlormethiazole*	(1.0G) 16	(<1.0G) 37
triazolam	(0.125mg+) 22	(<0.125mg) 20
thioridazine	(50mg+) 12	(<50mg) 24

*edisylate or equivalent

Table 7:9. Age distributions of hypnotic users receiving, and not receiving, other psychotropic drugs: (Survey 2)

	Age (years)				
	0-69	70-79	80-89	90+	Totals
No. (%) hypnotic users not receiving other psychotropic drugs	15(5.3)	76(27.0)	147(52.1)	44(15.6)	282
No. (%) hypnotic users receiving at least one other psychotropic drug	16(16.0)	41(41.0)	38(38.0)	5(5.0)	100

Chi-square = 24.6, df = 3, $p<0.001$

usage and age (chi-square = 5.1, df = 3, NS) or sex (chi-square = 0.6, df = 1, NS). Hypnotics were grouped into 14 categories. Eleven of these categories were of single drugs, and the remaining three contained compounds having pharmacological or therapeutic similarities. The frequency with which each category of drug was used is shown in Figure 7:4. The four most frequently used single drugs were further divided into "higher" and "lower" dose categories. For each of these drugs, the number of residents receiving "higher" and "lower" doses is shown in Table 7:8.

Of the 382 residents receiving hypnotics on the night of the survey, 100 (26.2%) were concomitantly receiving centrally acting medications (Table 7:9). These included phenothiazine major tranquillizers (40 cases), analgesics (18 cases), antidepressants (17 cases), benzodiazepine minor tranquillizers (12 cases), anti-convulsants (12 cases), and in one case, an antihistamine based expectorant. The use of these medications was significantly associated with the age of the recipients, hypnotic users who did not receive concomitant psychoactive medications tended to be older than those who did (chi-square = 24.6, df = 3, $p<0.001$).

Analysis of Factors Influencing Hypnotic Usage

The six indices of resident health status, and the five indices relating to home environment were categorized as "Resident Variables" and "Home Variables" respectively. Correlation

coefficients computed between prevalence rates and Resident Variables are shown in Table 7:11. No significant correlations were found between hypnotic usage and any of the five Home Variables. Of the six Resident Variables, hypnotic usage correlated significantly and negatively with the levels of mental illness, chairboundness, and incontinence within each home.

Subsequent analyses considered the survey population as a whole. From the total survey population, 431 individuals were negatively rated on all six indices of health status. This group, defined as non-Impaired, was used as a control against which to compare those rated positively on selected Resident Variables. These groups (the non-Impaired, and the Impaired) were considered in relation to hypnotic usage in 2 x 2 contingency tables (Table 7:12). Significant associations were present between hypnotic usage/non-usage and incontinence (chi-square = 11.02, df = 1, $p<0.01$), mental confusion (chi-square = 4.45, df = 1, $p<0.05$), and mental handicap (chi-square = 6.91, df = 1, $p<0.01$).

The most frequently rated impairment was that of physical handicap (441 individuals). Hypnotic usage within this group did not differ significantly from that within the non-Impaired group (Table 7:12). In a final analysis, those rated as physically handicapped were further sub-divided into those rated as physically handicapped and confused, and those rated as

Table 7:10. Correlation coefficients between Home Variables and levels of hypnotic usage within each home: (Survey 2)

Home Variable	Correlation Coefficient	n of Homes	p
percent male	-0.03	23	p<0.44
percent female	0.03	23	p<0.44
staff/resident ratio	0.09	23	p<0.33
GP/resident ratio	0.03	23	p<0.43
residents per home	-0.09	23	p<0.33

Table 7:11. Correlation coefficients between Resident Variables and levels of hypnotic usage within each home: (Survey 2).

Resident Variable	Correlation Coefficient	n of Homes	p
physical handicap	-0.33	23	p<0.06
mental handicap	-0.05	23	p<0.40
mental illness	-0.48	23	p<0.01 **
chairbound/ bedfast	-0.39	23	p<0.03 *
incontinent	-0.47	23	p<0.01 **
mentally confused	-0.30	23	p<0.09

Table 7:12. Levels of hypnotic usage within each Resident Variable category: (Survey 2)

Resident Variable	Hypnotic Nonusers No. (%)	Hypnotic Users No. (%)	n of residents	Chi-square value with non-Impaired group
non-Impaired	274 (63.6)	157 (36.4)	431	
physical handicap	288 (65.3)	153 (34.7)	441	0.21 NS
mental handicap	32 (86.5)	5 (13.5)	37	6.91 **
mental illness	58 (67.4)	28 (32.6)	86	0.31 NS
incontinent	83 (81.4)	19 (18.6)	102	11.02 **
mentally confused	165 (72.1)	64 (27.9)	229	4.45 *

Table 7:13. Levels of hypnotic usage within physically handicapped confused, and physically handicapped non-confused groups

	Hypnotic Nonusers No. (%)	Hypnotic Users No. (%)	n of residents	Chi-square value
physically handicapped confused	60 (72.3)	23 (27.7)	83	
physically handicapped non-confused	228 (63.7)	130 (36.3)	358	1.84 NS

* = $p<0.05$ ** = $p<0.01$ NS = not significant

physically handicapped and not confused. Hypnotic usage within these two groups did not differ significantly (Table 7:13). The relevance of this latter analysis is explained in the discussion.

Discussion

Hypnotic Usage

The overall level of, and between home differences in, hypnotic usage show little variation over the 24 week inter-study period. In combination, these data suggest that many of the individual hypnotic users identified in Survey 1 are also represented in Survey 2, indicating long term prescribing strategies in the treatment of sleep disorders in the elderly. The absence of a significant gender difference in hypnotic drug usage shown in Survey 1, is again shown in Survey 2. This finding reinforces the conclusion that the greater usage of hypnotics among elderly females in the community may be predicted from factors other than sex per se.

While the age distribution of hypnotic users is similar for both surveys, a significant relationship between age and usage did not emerge in the second study. The age related use of concomitantly prescribed centrally acting medications, however, indicates the existence of differing clinical needs, predictable from further age parameters, within this elderly population. It is a matter of some concern, however, that the very elderly (i.e. those 80-89y), irrespective of sex, were the group most

likely to receive more than one psychotropic drug. Williamson and Chopin (1980), for example, have recently confirmed the intuitively plausible prediction that the occurrence of adverse drug reactions in the elderly is directly related to the number of drugs prescribed.

The pattern of hypnotic drug usage is also similar for both studies, with nitrazepam being most frequently used. In the second survey, the category "Major/Minor Tranquillizers" was analyzed in more detail, viz. as chlormethiazole, diazepam, chlordiazepoxide, and other phenothiazines. It can be seen from Figure 7:4 that phenothiazines and nitrazepam represented almost half of the total hypnotic usage. The widespread use of phenothiazine major tranquillizers in single night-time doses may, in part, reflect an attempt to exploit the sleep inducing properties of drugs prescribed for a primary psychiatric condition. However, the low level of mental illness reported for hypnotic users (only 28 individuals, see Table 7:12) suggests that, in many cases, phenothiazines are employed as the night sedation of choice for this age group, irrespective of psychiatric status. The widespread use of thioridazine in particular, clearly shown in Survey 2 (Table 7:8), serves to emphasize this point.

In both surveys, a substantial minority of the individuals prescribed nitrazepam received a (10mg) dose contraindicated in this age group (Data Sheet Compendium, 1980-81). It is interesting to note also that nitrazepam was the most consistently

prescribed hypnotic; in Survey 2, variations in total hypnotic usage across homes (Figure 7:3) correlated significantly with across-homes variations in nitrazepam usage ($r = 0.4$, $n = 23$, $p<0.05$). Neither survey shows an overall preference for prescribing short half-life hypnotics. Nevertheless, three of the drugs shown in Figure 7:3 (representing 34.1% of total hypnotic usage) have been experimentally evaluated in, and recommended as suitable for, the elderly, viz. triazolam (Reeves, 1977), chlormethiazole, and temazepam (Briggs et al. 1980). As shown in Table 6:4, hypnotics are frequently prescribed for years rather than weeks or months. Under these circumstances, patients may develop a preference for a particular hypnotic drug, and resist its being substituted or withdrawn. Thus, it is possible that the trends in hypnotic usage shown in these surveys are not representative of the drug regimes which may be commenced at the present time. With regard to the drugs currently used, the concomitant use of centrally acting medications, and, in some cases (e.g. nitrazepam) the choice of dose, the overall pattern of hypnotic usage shows no consistent approach to the problem of minimizing adverse behavioural reactions to hypnotic drugs in the elderly.

Factors influencing Hypnotic Usage

The analyses presented in Table 7:10 tested the possibility that between-homes variations in levels of hypnotic drug usage

may be related to specific characteristics of the home environment. The absence of a significant relationship between Home Variables and hypnotic usage (Table 7:10) does not necessarily imply, however, that environmental factors do not influence hypnotic drug prescribing. The five factors analyzed possibly represent only single components in a complex chain of influences, many aspects of which were not recognized in the current analyses. Indices of resident health status, on the other hand, showed two levels of association with hypnotic drug usage. First, at the level of the home, variations in hypnotic usage were inversely related to the prevalence of mental illness, incontinence, and bedfast/chairboundness (Table 7:11). Second, at the level of the individual, ratings of incontinence, confusion, and mental handicap were all associated with a reduced probability of receiving hypnotic drugs relative to the unimpaired group (Table 7:12).

The negative correlations between hypnotic usage and reduced health status suggest the existence of a positive relationship between superior health status (low dependency) and hypnotic drug use. Similarly, when compared with the confused, the mentally handicapped, and the incontinent (Table 7:12) non-Impaired individuals show a significantly higher probability of receiving hypnotics. Accepting that positive or negative ratings on these dichotomous variables reflect differing degrees of general physical dependency, these findings are consistent with a conclusion that, in institutional settings, the less dependent residents tend to be more likely to receive hypnotic drugs.

Prevalence rates reported for hypnotic drug prescribing among the elderly in the United Kingdom (and reviewed in Chapter 6) vary from approximately 10% (Murray et al. 1981) to 27% (Skegg et al. 1978). In relation to these levels, the present data may be interpreted as showing a relative increase in hypnotic usage among the non-Impaired elderly in residential care, rather than a relative decrease in usage among the more dependent, less healthy, residents.

This relationship between dependency and hypnotic drug usage was considered in the final analysis (Table 7:13). The most frequently rated impairment, physical handicap, showed no association with hypnotic usage (see Table 7:12). This broadly-defined health status category included deafness, arthritis, cardiovascular disease, and limb-loss. Such a grouping would include individuals of widely differing degrees of dependency. If, then, hypnotic drug usage in the present study was related to dependency, this group should demonstrate similarly wide variations in hypnotic usage if appropriately sub-divided. To test this possibility, the physically handicapped group was further sub-categorized as described above, and as shown in Table 7:13. Those rated as physically handicapped and confused, and those rated as physically handicapped and not confused were considered as high dependency, and lower dependency groups respectively. In the event, hypnotic usage within these two sub-groups did not differ significantly. However, it can be seen from Table 7:13 that hypnotic usage within the physically handicapped

confused and non-confused cells is almost identical with that of the confused and non-Impaired groups respectively shown in Table 7:12. Thus, while Table 7:13 does not significantly confirm the conclusion that lower degrees of dependency are associated with a higher probability of receiving hypnotics, the trend shown <u>is</u> in the predicted direction.

These analyses indicate that, within residential homes for the elderly, there exist low dependency groups having a high probability of being prescribed, and of receiving, hypnotic drugs. It is interesting to note that a similar observation has been reported by Ingman et al. (1975) for "intermediate care facilities" for the elderly in the USA. Various factors, acting singly or in combination, might account for this relationship. Disturbed sleep in a residential home can arise from several causes (for example, unfamiliar surroundings, sharing a room, departures from established daily routines, etc.). If such problems are, as has been suggested by Herford (1982), selectively referred by the staff to the general practitioner, then it is possible that the prescribing of hypnotic drugs is, to some extent, mediated by the staff's perception of need. It is plausible that the needs of the least dependent, perhaps more demonstrative, residents are better communicated to the staff than are the needs of more dependent individuals. As Clarke et al. (1982) have pointed out, care staff draw the attention of general practitioners to the needs of the resident as a relative might if they were at home.

Conclusions

The design of the present study ensured that the information collected was of drugs actually administered. The levels of hypnotic drug usage shown in both surveys emphasize the value of, and the need for, relevant psychopharmacological assessments of sedative-hypnotic products likely to be prescribed for elderly individuals. However, it is also apparent that such information, where available, has, at the present time, less of an impact on prescribing trends than is desirable. Several published studies (reviewed in Chapter 5), for example, indicate that the elderly are particularly sensitive to the cumulative, residual effects of nitrazepam, especially in 10mg doses. The above surveys, however, show nitrazepam to be the most consistently and the most popularly used hypnotic drug.

As regards the design of further experimental studies, two specific points, emerge from these surveys. First, considering all drugs, the data suggest long term, repetitive use of sedative-hypnotic products by the elderly. Simulating this pattern of usage under controlled conditions demands a multiple-dose, and not a single-dose, design. Second, the dosage distributions for nitrazepam (shown in Tables 7:3 and 7:8) reflect the assumption, reported by Castleden et al. (1977), that the adverse behavioural effects arising from the use of this drug in 10mg doses by the elderly may be modified by employing a lower (5mg) dose. As a consequence of the information provided in the above surveys, this assumption will be experimentally analyzed in some detail in the

next two chapters.

Chapter 8

Experiment 2: An evaluation of the effects of single and repeated low doses of nitrazepam on performance in the elderly.

In Chapter 5 it was noted that nitrazepam, in night time doses of 10mg, has been reported to impair the daytime performance of both healthy (Castleden et al. 1977) and hospitalized (Linnoila and Viukari, 1976) elderly individuals. The survey data presented in the previous chapter showed that, although nitrazepam is still widely prescribed for the elderly, a dose of 5mg was recorded for the majority of recipients. This finding is consistent with the recommendations of Castleden et al. (1977) that "the dose of nitrazepam should be decreased in elderly patients". However, the assumption that adverse behavioural reactions to this drug in healthy elderly individuals can be significantly offset by employing a lower dose is not empirically supported.

The clinical literature contains few studies concerned with the effects of low dose nitrazepam on performance in the elderly. Nayal et al. (1978) compared the effects on psychomotor performance of single dose nitrazepam 5mg and chlormethiazole (base) 384mg in 18 rehabilitating medical geriatric inpatients. While performance, as measured by a letter cancellation task, did not differ significantly between the two drug conditions, it is relevant to note that this study did not include a placebo control and does not, therefore, represent a definitive evaluation of low dose nitrazepam in the elderly. Furthermore, the effects of drug accumulation, inherent in long half-life hypnotics like nitrazepam, are not evaluated in single dose studies. Witts et

al. (1979), for example, report computer predictions of nitrazepam plasma concentrations in the elderly which suggest that peak concentrations may more than double between the first and seventh repeated doses of this drug (i.e. from approximately 100 ng/ml after dose 1, to over 250 ng/ml after dose 7). Extrapolating from these data, it is reasonable to assume that residual concentrations will similarly increase with repeated doses. Two studies have reported the effects of repeated low doses of nitrazepam in elderly hospital patients. Viukari et al.'s (1978) comparison of the effects of repeated dose flurazepam 15mg, fosazepam 60mg, and nitrazepam 5mg (discussed in Chapter 5) in psychogeriatric inpatients does report a significant slowing of tapping speed during the nitrazepam condition. Results from this severely impaired patient group, however, which included individuals with diagnoses of senile dementia, cerebral arteriosclerosis, Korsakov's psychosis, and schizo-affective psychosis, do not readily generalize to those elderly persons who receive primary medical care from general practitioners. Murphy et al.'s (1982) data, which suggest impaired performance on a card-sorting task in medical geriatric inpatients following five repeated doses of nitrazepam 2.5mg, present similar problems of generality. Furthermore, the design of this latter study (critically reviewed in Chapter 5), which compared the effects of nitrazepam and triazolam 0.125mg, did not include a placebo control. The decrements reported, therefore, are relative only to the effects of repeated dose triazolam.

In healthy young adults, nitrazepam 5mg has been associated with few residual effects on performance. Malpas et al. (1970)

compared performance on the Crossman card-sorting task in 12 male subjects (aged 18-24y) 13h after the ingestion of single dose nitrazepam 5mg or 10mg, and placebo. No significant effect was reported following nitrazepam 5mg on measures of movement or choice reaction times, while a significant slowing of movement time was reported for the larger, 10mg dose. Bond and Lader (1972) compared the residual effects of single dose nitrazepam 5mg and 10mg in 10 healthy subjects (aged 21-34y). Tests included choice reaction time, simple reaction time, tapping speed, letter cancellation, digit symbol substitution, and the Gibson spiral maze. While nitrazepam 10mg significantly impaired performance on the simple reaction time, tapping speed, and digit symbol substitution tests, only digit symbol substitution showed impairment following the 5mg dose. In young adults, then, nitrazepam in single 5mg doses is clearly associated with a reduced probability of residual sequelae. In the present study, the effects of single and repeated low doses of nitrazepam on the performance of healthy elderly people are evaluated and compared.

A further purpose of the present study was to pilot an experimental methodology for assessing the residual effects of hypnotic drugs in the elderly. Methodological considerations relevant to the design of, and selection of tests for psychopharmacological performance studies involving elderly subjects have been discussed in Chapter 5. These considerations, which have been recognized in the design of the present experiment, will be re-emphasized where appropriate.

Methods

Subjects

All subjects were resident within local authority homes for the elderly in the Edinburgh area. Two men (aged 77 and 79y) and ten women (aged 76, 77, 80, 84, 85, 86, 88, 89, 91, and 96y) participated on a voluntary basis. The group mean age was 84.0y. None was receiving psychoactive medication, and each abstained from alcohol for the duration of the study. All subjects were in good general physical health, and each participated with the consent of their own general practitioner, and with the consent and cooperation of Lothian Regional Social Work Department. Prior to their inclusion in the study the mental and physical competence of each subject was assessed using the Survey Version of the Clifton Assessment Procedures for the Elderly (Pattie and Gilleard, 1979). These procedures include the assessment of physical disability (PD) which is expressed as a PD score, and general mental competence, which is expressed as an information/orientation (I/O) score. In both cases, high scores indicate low dependency, and vice versa. The PD score is then deducted from the I/O score, and the resultant value is converted into an overall grading, which can range from Grade A ("No impairment") to Grade E ("Severe impairment - maximum dependency"). Grades A or B were achieved by all participating subjects. These selection procedures were employed for two reasons. First, to exclude individuals with significant mental

or physical impairment, and second, to reduce variability in the group as regards mental and physical abilities.

Experiment Design

The design of the experiment is shown in Diagram 8:1. A double-blind, group controlled design was used to reduce the duration of the experiment, and thus reduce the risk of subject drop-outs. [It was felt that an alternative within-subjects design, which included practice, baseline, and washout periods, and which would have taken proportionately longer to administer, would have increased the probability of drop-outs in this high-risk elderly group]. Subjects were blind to the experimental conditions throughout the study; the experimenter was blind to the experimental conditions only between nights 15-22 (Diagram 8:1).

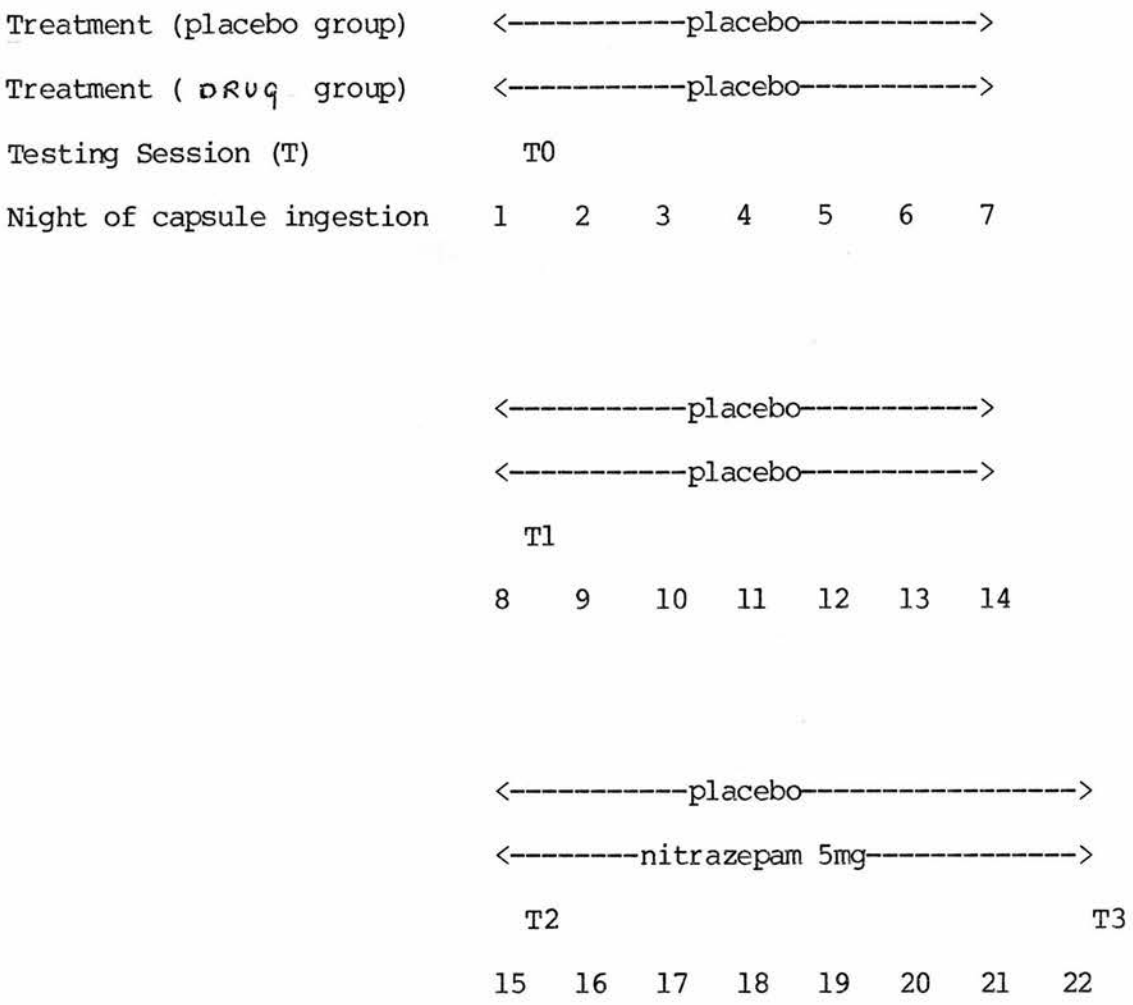


Diagram 8:1 Experiment design and testing schedule

Subjects were randomly assigned to the control or drug groups (n = 6/group) with the single constraint that each group should contain one male. Both groups received identical capsules on 22 consecutive nights. For the drug group, capsules contained placebo on nights 1-14, and nitrazepam 5mg on nights 15-22. The control group received placebo throughout. Testing sessions commenced on the morning following the first administration of

capsules, and then at regular weekly intervals for the succeeding three weeks. Thus, the drug group was tested twice under placebo conditions, the morning after the first, and the morning after the eighth consecutive dose of nitrazepam. Each subject was tested 12-14h after receiving a capsule. Test sessions were conducted in a performance laboratory at the Royal Edinburgh Hospital. Subjects attended the laboratory in groups of six, and were individually tested in turn. The same order of testing was maintained throughout the experiment.

Before commencing the experiment proper, each subject received two informal practice sessions on the test apparatus described below. These practice periods, conducted within the residential homes, allowed the subjects to gain familiarity with the requirements of the task.

Testing Procedure

The main criteria for the selection of an appropriate performance task were as follows:

1) the task should measure both the speed, and the accuracy of performance;

2) the amount of potentially irrelevant stimuli generated by the task should be minimal;

3) the demands of the task (i.e. the degree of task complexity) should be variable;

4) efficient performance on the task should not require a level of manual dexterity outwith the physical competence of very

elderly individuals. (This latter criterion effectively precluded many tests which load heavily on writing skills).

A task which met all these criteria was a modification of the reciprocal tapping task described by Fitts (1954), and subsequently employed in aged populations by Welford et al. (1969). In the present experiment the apparatus consisted of a metal board (20.5cm x 45.5cm) into which could be fitted identical pairs of metal disks (targets), which were placed 25cm apart (centre to centre). These targets were symmetrically placed in the mid-line of the board. A diagram of this apparatus is shown in Appendix 5:1. The subject was provided with a pen-like contact stylus and required to tap each target alternately as quickly, and as accurately as possible over a 30s period. Contacts with either of the two targets (hits) or with the surrounding fascia (errors) completed an electric circuit and registered on an appropriate digital counter. Three different target sizes were used: 6cm; 4cm; and 1.5cm diameters. These three pairs of targets were presented first in descending order, and then in ascending order of size. Scores were averaged over ascending and descending presentations. A constant time interval of 1 minute was observed between each 30s trial. The subject used the preferred hand.

Two measures were recorded from this task:

1) mean total contacts (hits + errors) for each target size;

2) mean total errors for each target size.

Subjective Ratings

Throughout the study Home staff completed, according to their own observations and judgement, daily ratings of the subject's general behaviour. The 10cm visual analogue scales used for this purpose are reproduced in Appendix 5:2. Five subjective variables were rated: Sleep Quality, "better than usual" to "worse than usual"; Morning Alertness, "very alert" to "very drowsy"; Daytime Alertness, "extremely bright and alert" to "generally lethargic and drowsy"; Steadiness of Gait, "more steady than usual" to "less steady than usual"; and Mental Competence, "extremely lucid and clear" to "generally confused".

Analysis of Data

The first test session (T0, Diagram 8:1) was for adaptation and practice only. Data from the remaining three sessions were analyzed by repeated measures analysis of variance with one grouping factor (drug/placebo) and two trial factors (test sessions 1, 2, and 3; target sizes 6cm, 4cm, and 1.5cm). As test session 1 was a placebo condition for both groups, drug effects, if present, were expected to emerge as interactions between session and group, rather than as main effects of group alone. Where appropriate, paired comparisons were subsequently undertaken using t-tests for independent samples. Two tailed tests of significance were used throughout.

Further analyses were then undertaken to evaluate the sensitivity of the task at all three levels of task complexity. Unweighted deviation scores for each target condition (6cm, 4cm, and 1.5cm) were calculated by deducting a given subject's scores for test sessions 2 and 3 from that subject's appropriate scores for test session 1. Deviation scores for each of the three target sizes were then individually analyzed by repeated measures analysis of variance with one grouping factor (drug/placebo) and one trial factor (test session 2 and 3).

Subjective Ratings

Daily ratings collected during a seven day period following the eighth night of capsule ingestion (see Diagram 1) were considered as baseline data. For each of the five subjective variables, each subject's mean baseline score for this period was calculated. Unweighted deviation scores were then calculated for each rating collected during the seven day period following the 15th night of capsule ingestion. This latter period corresponds to the first seven days of nitrazepam ingestion by the drug group. For each individual day within this period, and for each subjective variable, deviation scores (calculated as the mean baseline score minus the subsequent raw score) from the drug and placebo groups were compared using the Mann-Whitney U test.

Results

One female subject (age = 86y) in the placebo group withdrew from the experiment in the second week owing to a chest infection. The mean age of the remaining 11 subjects was 83.8y. (drug group, n = 6; mean age = 83.5y; control group, n = 5, mean age = 84.2y)

Analysis of mean total contacts for all three target conditions (Table 8:1) showed no significant main or interaction effects which distinguished performance in the drug group from that in the placebo group. Analysis of mean errors, however, (Table 8:2) showed a significant group by session interaction ($F = 6.92$; $df = 2,18$; $p<0.01$). This interaction is illustrated in Figure 8:1. From this figure it can be seen that mean errors increased under the nitrazepam condition. Results from paired comparisons between the groups for each of the three test sessions are presented in Table 8:3. These results show that differences between the groups reached significance in session 3 ($t = 2.38$; $p<0.05$). [Havlicek and Peterson (1974) have demonstrated that the t value remains an effective and robust index of differences between means where group sizes differ only slightly, and where n = 5 in one of the groups].

Analyses of the deviation scores for each individual target size are presented in Tables 8:4 (6cm targets), 8:5 (4cm targets), and 8:6 (1.5cm targets). For the target sizes 6cm and 4cm, error deviation scores showed no significant main or interaction effects which distinguished performance in the drug group from that in the placebo group. Analysis of error deviation

Table 8:1 Analysis of variance of mean total contacts (reciprocal tapping task)

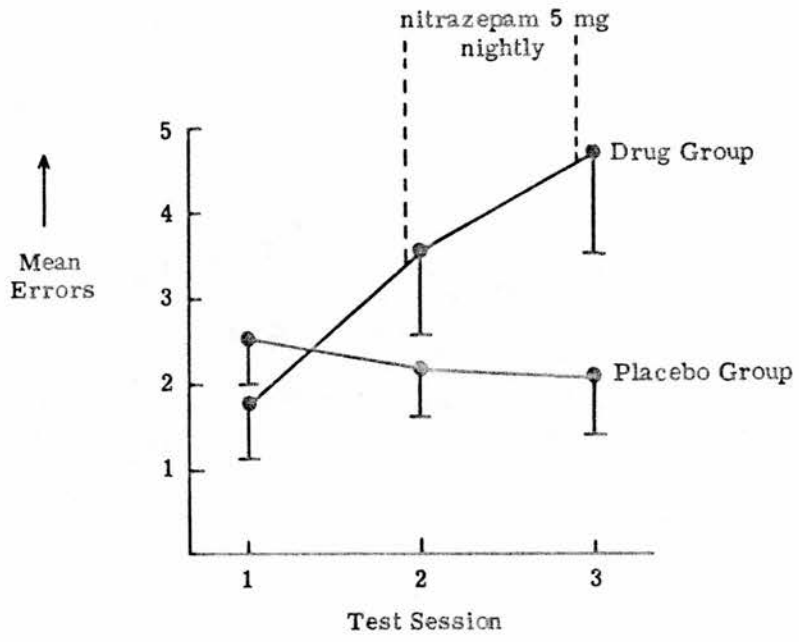
Source	Sum of Squares	df	Mean Square	F	p
Mean	91488.975	1	91488.975	298.74	0.000
Group (G)	56.324	1	56.324	0.18	0.678
Error	2756.265	9	306.252		
Session (S)	204.927	2	102.464	8.17	0.003
S x G	55.624	2	27.812	2.22	0.138
Error	225.738	18	12.541		
Target (T)	164.586	2	82.293	4.18	0.032
T x G	14.200	2	7.100	0.36	0.702
Error	354.087	18	19.671		
S x T	61.607	4	15.402	1.75	0.162
S x T x G	11.038	4	2.760	0.31	0.868
Error	317.735	36	8.826		

Table 8:2 Analysis of variance of mean total errors (reciprocal tapping task)

Source	Sum of Squares	df	Mean Square	F	p
Mean	798.000	1	798.000	34.24	0.000
Group (G)	27.445	1	27.445	1.18	0.306
Error	209.768	9	23.308		
Session (S)	26.416	2	13.208	3.64	0.047
S x G	50.214	2	25.107	6.92	0.006
Error	65.346	18	3.630		
Target (T)	269.648	2	134.824	11.73	0.001
T x G	20.658	2	10.329	0.90	0.425
Error	206.857	18	11.492		
S x T	89.249	4	22.312	4.91	0.003
S x T x G	35.996	4	8.999	1.98	0.119
Error	163.670	36	4.546		

Group = drug group/placebo group
Session = test session 1, 2, and 3
Target = 6cm, 4cm, and 1.5cm diameters

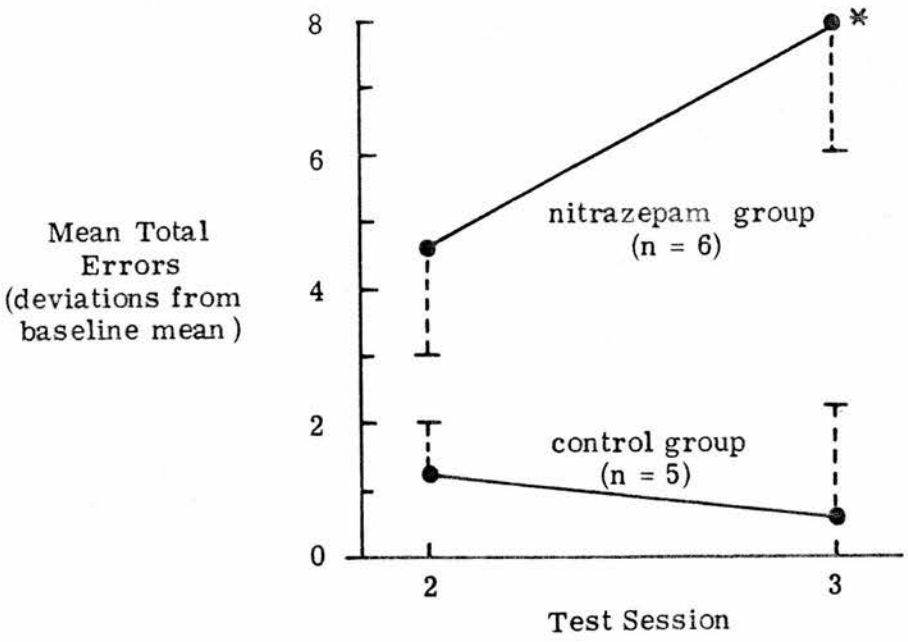
RECIPROCAL TAPPING TASK : MEAN TARGET ERRORS



Session x Drug: $F = 6.92$; $df = 2, 18$; $p < 0.01$

Figure 8:1 Effects of single, and eight repeated doses of nitrazepam 5mg on perfromance in the elderly

RECIPROCAL TAPPING TASK : FREQUENCY OF ERRORS OVER 30s PERIOD



$p < 0.05$

Figure 8:2 Effects of single, and eight repeated doses of nitrazepam 5mg on performance in the elderly (deviation scores)

Table 8:3 Paired comparisons between drug and placebo groups: reciprocal tapping (mean total errors)

Test Session	Mean Errors (SD) drug group	Mean Errors (SD) placebo group	t-value
1	1.78 (1.33)	2.60 (1.21)	1.08
2	3.58 (2.73)	2.23 (1.21)	1.09
3	4.78 (2.36)	2.13 (1.24)	2.38*

* = $p<0.05$

Table 8:4 Analysis of variance of mean error deviation scores: reciprocal tapping task (6cm Targets)

Source	Sum of Squares	df	Mean Square	F	p
Mean	4.097	1	4.097	0.43	0.529
Group (G)	22.552	1	22.552	2.36	0.159
Error	86.017	9	9.557		
Session (S)	2.933	1	2.933	1.11	0.320
G x S	1.024	1	1.024	0.39	0.549
Error	23.817	9	2.646		

Table 8:5 Analysis of variance of mean error deviation scores: reciprocal tapping task (4cm Targets)

Source	Sum of Squares	df	Mean Square	F	p
Mean	0.947	1	0.947	0.28	0.608
Group (G)	6.402	1	6.402	1.91	0.200
Error	30.167	9	3.352		
Session (S)	5.638	1	5.638	1.75	0.219
S x G	0.547	1	0.547	0.17	0.690
Error	29.067	9	3.230		

Group = drug group/placebo group
Session = test session 1, 2, or 3

Table 8:6 Analysis of variance of mean error deviation scores: reciprocal tapping task (1.5cm Targets)

Source	Sum of Squares	df	Mean Square	F	p
Mean	286.046	1	286.046	16.30	0.003
Group (G)	155.637	1	155.637	8.87	0.015
Error	157.954	9	17.550		
Session (S)	10.064	1	10.064	1.07	0.328
S x G	23.109	1	23.109	2.54	0.152

Table 8:7 Analysis of variance of mean total contacts as deviation scores: reciprocal tapping task (1.5cm Targets)

Source	Sum of Squares	df	Mean Square	F	p
Mean	530.558	1	530.558	12.50	0.006
Group (G)	77.217	1	77.217	1.82	0.210
Error	381.897	9	42.433		
Session (S)	25.508	1	25.508	4.39	0.066
G x S	1.167	1	1.167	0.20	0.665
Error	52.322	9	5.814		

Session = test session 1, 2, or 3
Group = drug group/placebo group

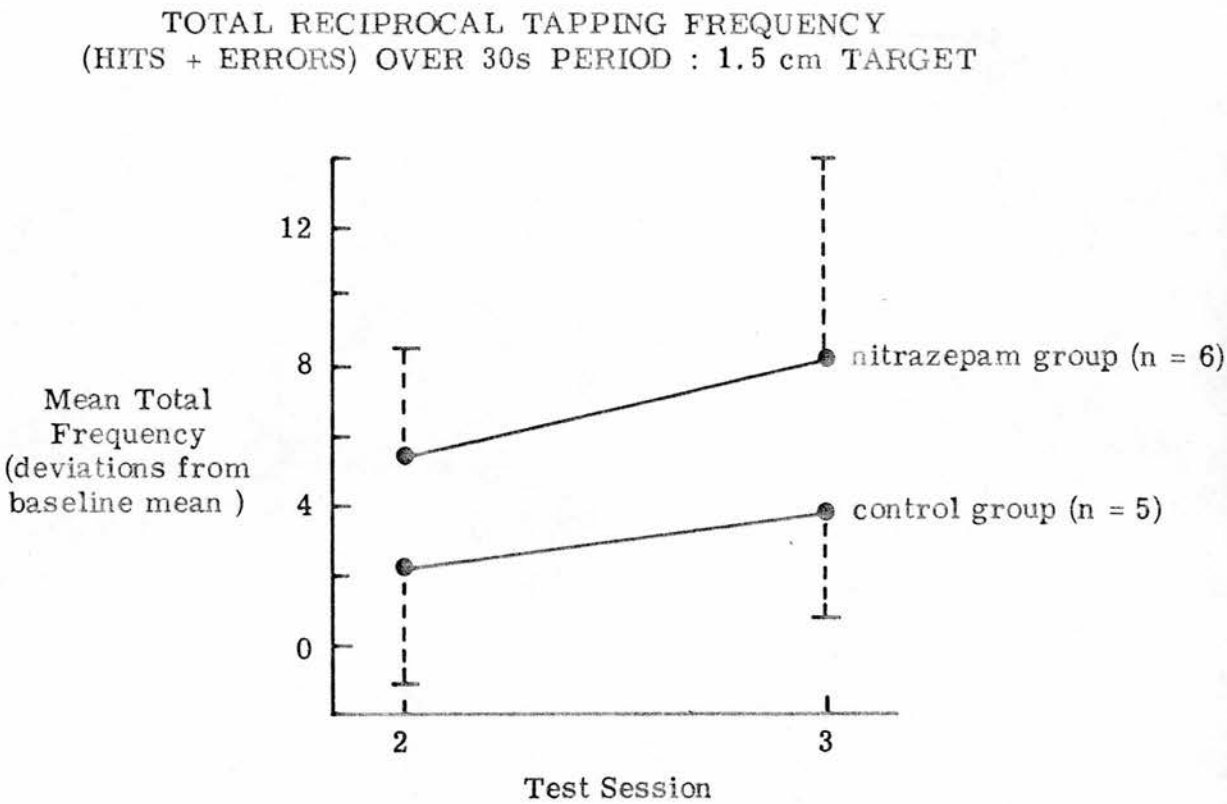


Figure 8:3 Effects of single, and eight repeated doses of nitrazepam 5mg on frequency of tapping in the elderly

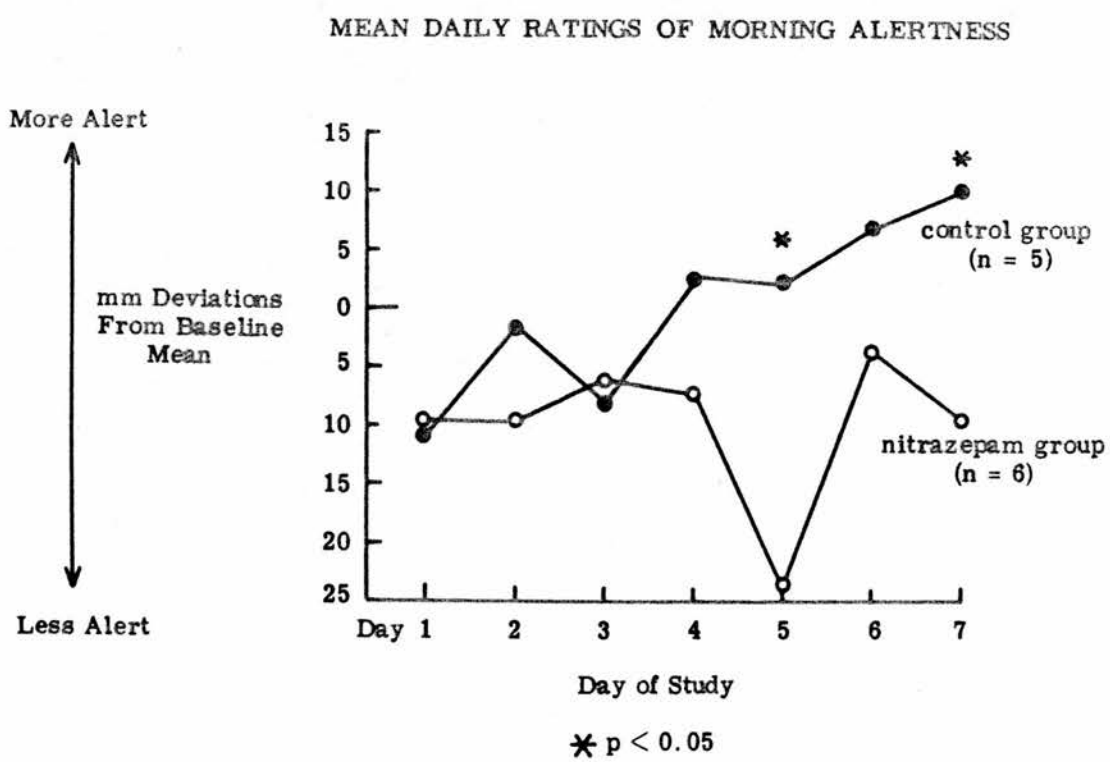


Figure 8:4 Effects of nitrazepam 5mg on daily ratings of morning alertness

scores for the 1.5cm target condition, however, showed a significant main effect of group ($F = 8.87$; $df = 1,9$; $p<0.05$). Figure 8:2 shows that, for the 1.5cm targets, the placebo condition was associated with superior performance. The analysis of total contacts (as deviation scores) for the 1.5cm target condition is shown in Table 8:7, and illustrated in Figure 8:3. Analysis of variance of these scores showed no significant main or interaction effects which distinguished performance in the drug group from that in the control group.

Subjective Ratings

For ratings of Sleep Quality, Daytime Alertness, Steadiness of Gait, and Mental Competence, scores varied little from day to day. None of these variables showed systematic differences between the drug and placebo groups. However, for ratings of Morning Alertness, differences between the groups did show a trend towards significance in the latter part of the week. The mean daily scores for morning alertness are shown in Figure 8:4. On this variable, scores differed significantly on the mornings following the 5th ($U = 4.5$, $p = 0.05$) and the 7th ($U = 3.0$, $p = 0.03$) dose of nitrazepam in the drug group

Discussion

On the reciprocal tapping task, the overall frequency of tapping, as measured by total contacts, reflects the speed of the

subject's performance, while the error score indicates the degree of accuracy. Increased accuracy on this task may be achieved at the cost of speed, and vice versa. In the present experiment, repeated low doses of nitrazepam 5mg impaired psychomotor accuracy, but did not significantly affect the speed of motor responses in this elderly group. The significant increase in errors shown by the drug group between test sessions 2 and 3 (Figure 8:1), is consistent with drug accumulation during this period. Table 8:2 shows no interaction between Target and Group ($F = 0.90$; $df = 2, 18$; $p = 0.425$), suggesting that impairment was independent of the differing demands of the task. However, such an interaction may have been attenuated by the inclusion of test session 1 (placebo for both groups) in the analysis. Results from the analysis of deviation scores (Tables 8:4, 8:5, and 8:6) suggest, rather, that the smallest target size (1.5cm) was most sensitive to the drug effects shown here. That repeated doses of nitrazepam 5mg selectively affected accuracy on this task is again emphasized in Figures 8:2 and 8:3. While both groups showed similar levels of psychomotor speed on, and similar levels of improvement between, test sessions 2 and 3 (Figure 8:3), the drug group showed a marked and significant decrease in accuracy over the same period (Figure 8:2).

As noted in Chapter 5, elderly individuals are adept at improving their accuracy on sensory-motor tasks by making compensatory reductions in their speed of performance. Kay (1955), for example, reports that on relatively simple tasks, the elderly tend to be slower, but more accurate than younger

subjects. It is reasonable to assume, then, that reductions in tapping efficiency (i.e. an increase in errors), if perceived by the subject, would result in a compensatory slowing of performance. Thus, subjects in the drug group could have maintained error scores at about pre-drug levels had they reduced their frequency of tapping. Clearly, however, this did not occur. Following both the first, and the seventh repeated doses of nitrazepam, subjects in the drug group maintained a frequency of tapping incompatible with efficient performance (as defined by their own baseline values). Such a result may relevantly be considered in terms of impaired judgement of accuracy.

The reciprocal tapping task provides the subject with no augmented feedback. Thus, in order to monitor the efficiency of their own progress, subjects must rely on visual, and proprioceptive cues. This process corresponds to the subjects "judgement of accuracy", and can be assumed to mediate the selection of tapping frequency (Welford, 1980). Should this judgement be impaired, then it is possible that subjects will be less aware of their own errors and, as a consequence, fail to compensate for them. In this respect it is particularly relevant to note that performance in the control group (Figure 8:1) deviated little between sessions 1 and 3, suggesting that, after practice on this task, these elderly subjects selected, and maintained their optimal "trade-off" between speed and accuracy throughout the study. Support for this conclusion is provided by the data of Salem et al. (1981) who report that the time taken to complete the Gibson spiral maze was increased in elderly females

11h after a single dose of nitrazepam 10mg, while accuracy was unimpaired at this time. Unlike the reciprocal tapping task used in the present experiment, errors on the Gibson spiral maze are clearly and permanently visible to the subject, and probably allow more efficient monitoring of performance and compensatory reductions in speed. [The Gibson spiral maze, fully described in the next chapter, requires the subject to track through a printed maze with a pencil. Contact between pencil and the "walls" of the maze constitute errors].

Ratings of early morning alertness also show a pattern of results which, in part, are consistent with cumulative drug effects over the seven day period. This result, however, must be interpreted with some caution. It can be seen from Figure 8:4 that deviation scores for the control group suggest an increase in alertness between the first and seventh days of recording. Nevertheless, mean scores in the drug group remain below baseline levels throughout this period. If the placebo scores reflect a response bias in the raters, such a bias may have been "corrected" by an overt drug-induced reduction in morning alertness in the nitrazepam group.

The absence of any significant effects on staff ratings of sleep quality does not challenge the known hypnotic efficacy of nitrazepam in middle-aged (Adam et al. 1976) and elderly (e.g. Haider, 1967, 1968; Linnoila and Viukari, 1976) individuals. These particular ratings were scored by the night staff on the basis either of personal judgement, or by replies elicited from the subjects. In general, these visual analogue scales showed a

marked tendency for staff to favour a "no change" score throughout the experiment, suggesting an absence even of normal variations in sleep quality. While the ratings used in the present study were a departure from the, apparently more sensitive, instruments used in Experiment 1 (and described in Chapter 4), they nevertheless served the important function of focussing the attention of the staff on to this high-risk elderly group during the course of the experiment.

Conclusions

The results from the present study challenge the assumption that adverse behavioural reactions to nitrazepam in the healthy elderly can be effectively offset by employing a 5mg dose. While impaired performance was not apparent after a single 5mg dose, repeated doses clearly disrupted the efficiency of performance in this elderly group. This effect was consistent with drug accumulation over the seven day experimental period, and might plausibly be attributed to the subject's impaired judgement of error.

Support for this conclusion is provided by the recently published study of Cook (1983), in which single and repeated doses of temazepam 20mg, and nitrazepam 5mg, were evaluated and compared in 58 rehabilitating hospital inpatients. Both nitrazepam and temazepam were associated with worsening performance on a choice reaction time task between the first and seventh nights of drug consumption (see Table 5:1). Pharmacokinetic data from this study

show that the mean residual concentrations of both drugs increased over the seven day drug taking period: from 126 ng/ml to 190 ng/ml for temazepam; and from 23 ng/ml to 49 ng/ml for nitrazepam. A particularly interesting finding of Cook's (1983) study concerns performance on a letter cancellation task similar to that used by Castleden et al. (1977), and described in Chapter 5. Following both drug treatments, and relative to placebo scores, speed on this task was reported to be slower, while accuracy was reported to increase. Thus, under the drug conditions, subjects apparently improved their accuracy on the cancellation task by reducing speed. In the event, overall efficiency (as measured by time x errors) following both drug conditions did not differ significantly from placebo. These data reinforce the suggestion that drug impaired accuracy, if apparent to the subject, may be compensated for by a suitable reduction in speed.

At a methodological level, the present study has demonstrated the effectiveness of the reciprocal tapping task in assessing residual drug effects in the elderly. Both this task, and aspects of the present study design, are further developed in Experiment 3. Two specific points will be noted here. First, from the analyses of raw and deviation scores, it is apparent that both were sensitive measures of drug effects. Second, it is also apparent that the informal practice sessions conducted prior to the experiment proper, facilitated relatively steady levels of performance on the reciprocal tapping task. Together, these findings suggest that, in a conventional crossover design

experiment, the study duration can be reduced without loss of sensitivity by omitting practice or baseline sessions. These considerations are implemented in the design of the next experiment.

Footnote

It should be noted that the studies of Murphy et al. (1982) and Cook (1983) were reported after the above experiment had been designed and executed.

CHAPTER 9

Experiment 3: A comparison of the effects of repeated dose nitrazepam 5.0mg, lormetazepam 1.0mg and placebo on daytime performance in the elderly.

Introduction

The results from the previous experiment (Chapter 8) indicate that impairment of performance efficiency in the elderly may accompany the repeated use of long-acting hypnotics, even when low doses are specifically employed. The impairment shown was consistent with drug accumulation over the eight nights of consumption. Given this characteristic of the residual effect, it remains probable that (as argued in Chapter 2) repeated doses of short acting compounds, being less likely to accumulate, will also be less likely to impair daytime efficiency. This conclusion is supported by the results presented in Chapter 3; the effects on performance of repeated doses of triazolam (mean elimination half-life = 2-4h) and loprazolam (mean elimination half life = 15h) showed no evidence of drug accumulation over the 16 consecutive nights of consumption in middle-aged subjects. Nevertheless, repeated 0.5mg doses of the very short acting triazolam were associated with a relative increase in subjectively rated anxiety, a finding consistent with daytime withdrawal effects. So far as untoward behavioural reactions are concerned, then, it is reasonable to suggest that the optimal elimination half-life for an hypnotic drug lies within the range >4h to 15h. Within this

range repeated doses would be less likely to produce either cumulative effects, or possible daytime withdrawal effects, on performance. In the present experiment, this hypothesis is tested in elderly subject-volunteers; the effects on performance in the elderly of the short-acting hypnotic lormetazepam are evaluated, and compared with those of low-dose nitrazepam and placebo.

Lormetazepam [7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1, 3-dihydro-2H-1, 4-benzodiazepine-2-one] is a recently introduced benzodiazepine derivative. In healthy young adults (mean age = 24.2y) the mean plasma half-life is reported to be approximately 10h, while in healthy elderly individuals (mean age 65.8y) the mean plasma half-life is increased to approximately 15h (Humpel et al. 1982). Oswald et al. (1979) compared the hypnotic and residual effects of repeated dose lormetazepam and flurazepam in two groups of volunteers. During a three week period of drug consumption, EEG sleep recordings showed lormetazepam (2.5mg and 1.0mg) and flurazepam (30mg) to be effective hypnotics in nine middle-aged subjects (mean age = 61y). In a further 12 subjects (mean age = 53y) neither dose of LORMETAZEPAM was associated with significantly impaired performance on tests of auditory vigilance, manual dexterity, digit-symbol substitution, or card sorting following 16 consecutive doses. Flurazepam 30mg, over the same period, showed a pattern of worsening performance between the third and sixteenth doses consistent with drug accumulation. In a single dose study, however, Nicholson and Stone (1982) report that, while lormetazepam 0.5mg, 1.0mg and 2.0mg were all effective

hypnotics, the 2.0mg dose was associated with impaired performance on a visuo-motor coordination task (Borland and Nicholson, 1974) and on the digit-symbol substitution test in six healthy male subjects (mean age = 22y). The reasons for these discrepant results concerning higher doses of lormetazepam are obscure, though the possibility exists that Oswald et al.'s older subjects, who were all self-reported poor sleepers, actually derived some daytime behavioural advantage from the use of lormetazepam 2.5mg.

The impact of lormetazepam on the daytime performance of healthy aged subjects has not been investigated. In the present study, the effects of repeated dose lormetazepam 1.0mg, nitrazepam 5mg, and placebo are evaluated and compared. The study had three specific objectives.

First, to test the hypothesis that repeated doses of short-acting hypnotics, whose elimination half-life in the elderly falls within the range >4-15h, are less likely to be associated with impaired daytime performance in this age group.

Second, to replicate the results of Experiment 2 (Chapter 8) concerning the impact of low-dose nitrazepam on performance in the elderly.

And third, to further investigate the effects of repeated doses of hypnotic drugs on speed and accuracy in the elderly by extending the use of the reciprocal tapping task (Chapter 8) , and by including other tasks which measure these aspects of

performance. Thus, in addition to the reciprocal tapping task the present test procedures included the Gibson spiral maze (Gibson, 1978), and a letter cancellation task (as described by Briggs et al. (1980). Both tests have previously been used in studies concerned with the residual effects of hypnotic drugs in the elderly (Salem et al. 1982, and Briggs et al. 1980 respectively; see Table 5:1).

Subjects

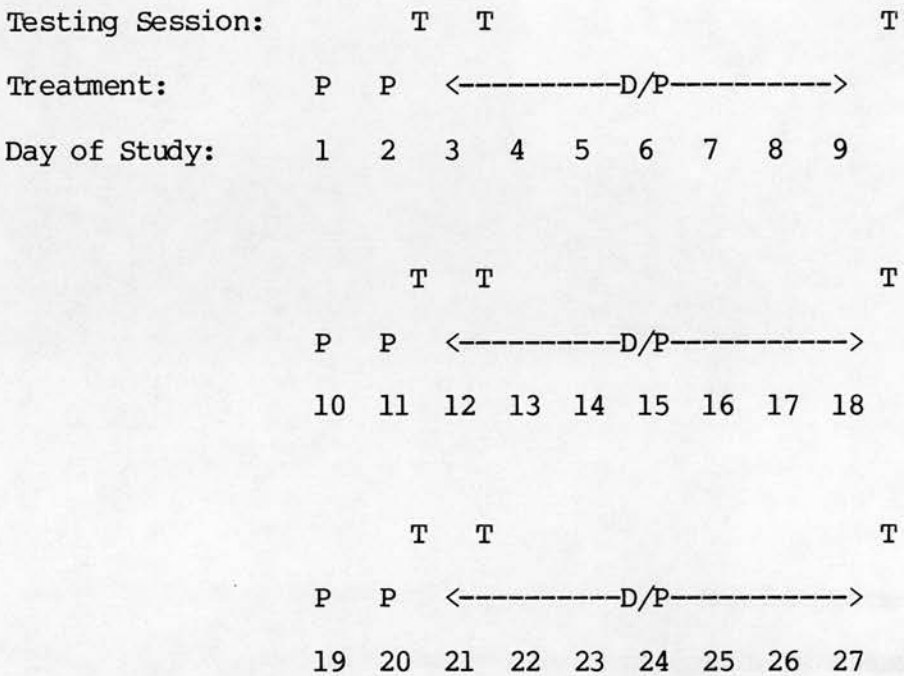
All subjects were resident within Local Authority Homes for the Elderly in the Edinburgh area. Three men (aged 80, 75 and 78), and nine women (aged 83, 96, 82, 79, 90, 78, 78, 81 and 77) participated. The group mean age was 81.4y. Each subject was paid on completion of the study. None was receiving psychoactive medication, and each abstained from alcohol for the duration of the study. All subjects were in good general physical health, and each participated with the consent of their own general practitioner, and with the consent and cooperation of Lothian Regional Social Work Department. Prior to their inclusion in the study the mental and physical competence of each subject was assessed on the Survey Version of the Clifton Assessment Procedures for the Elderly (Pattie and Gilleard, 1979). Grades of A or B were achieved by all participating subjects (see Chapter 8). These procedures were employed to exclude individuals with significant mental or physical impairment, and to reduce variability in the group as regards mental and physical abilities.

Design

The present study includes many of the design features employed in Experiment 2 (Chapter 8), particularly pre-experimental practice sessions, and experimental performance testing after single and multiple doses of drug. Unlike the previous experiment, however, baseline weeks were omitted from, and a within-subjects design was used in the present study.

Identical matching capsules of lormetazepam 1.0mg, nitrazepam 5.0mg, and placebo were administered in a within-subjects design experiment (Diagram 9:1). Subjects received each of these treatments for a period of seven nights, in a balanced double-blind sequence (see Diagram 9:1).

Each of the seven treatment nights was preceded by two nights of placebo. Thus, subjects received the capsules continuously for 27 nights. The sequence of performance testing is also shown in Diagram 1. A practice session followed the second placebo capsule prior to each treatment week. Each subjects was then tested on the morning following the first, and the morning following the seventh capsule within each drug week. Subjects were blind to the experimental conditions throughout the experiment; the experimenter was blind to the experimental conditions only during the Drug/Placebo weeks (Diagram 9:1).



T = Day of Testing Session

D = Drug (lormetazepam 1.0mg or nitrazepam 5mg)

P = Placebo

Diagram 9:1 Study design and testing schedule

Before commencing the experiment proper, each subject received two informal practice sessions on the tests described below. These practice sessions were conducted in the residential homes, in rooms subsequently used for experimental testing.

Method

Drugs were administered by senior care staff within each Home at the subject's normal bedtime. Each subject was tested 12-14h after receiving a capsule. A quiet room in which testing could be completed without interruption was allocated by the staff, and used on each testing occasion. The performance tests, which took approximately 25 minutes to complete, were as follows:

1. The reciprocal tapping task. (The apparatus for this task is described in Chapter 8, and Appendix 5:1). The subject was required to tap two identical circular targets placed 10 inches apart (centre to centre) alternately with a contact stylus as quickly and as accurately as possible over a 30-second period. Contacts with either target (hits) or with the surrounding fascia (errors) completed an electric circuit and registered on digital counters. Four different target sizes were used (2cm, 3cm, 4cm and 6cm diameters). Targets were presented first in descending order and then in ascending order of size. A constant time interval of one minute was observed between each trial. Scores for each target size were averaged over ascending and descending presentations. The subject used the preferred hand. Two measures were analyzed from this task.

   i. Mean total contacts (hits + errors) for each target size;
   ii. The mean percentage errors for each target size (i.e. [the mean total errors/mean total contacts] x 100)

2. The Gibson spiral maze (Gibson, 1978). This paper and pencil

test requires the subject to track through a simple spiral maze as quickly, and as accurately, as possible. The test was scored according to the manual (Gibson, 1978). The 15sec time stresses (i.e. verbal requests, made every 15sec, for the subject to proceed faster) have been found to be unsuitable in older populations (see Gilleard, 1982), and were therefore omitted. Three measures were recorded and subsequently analyzed.

i. The time taken to complete the maze.
ii. The error score (errors are scored when the "walls" of the maze are touched, or penetrated by the pencil).
and iii. The total efficiency score, calculated as time x (log (error + 1)).

3. A large print letter cancellation task (after Briggs et al. 1978). The subject was presented with a single page of large print prose (5.0mm characters) and asked to delete as many letter "e"s as possible over a two minute period. A different page was used on each testing occasion. A representative page is reproduced in Appendix 6:2. Three measures were analyzed from this task.

i. The total number of "e"s deleted (i.e. the number of hits).
ii. The total number of "e"s missed (i.e. the number of "e"s not deleted between the first and the last "e" successfully deleted).
iii. The number of "e"s deleted as a percentage of i + ii above.

Subjective Ratings.

Throughout the study Home staff completed, according to their own observations and judgement, daily ratings of the subject's level of morning alertness. Each morning throughout the study, subjects completed ratings of sleep quality. The 10cm visual analogue scales used for both ratings are reproduced in Appendix 6:1. Sleep quality was rated on a scale from "better than usual" to "worse than usual"; the scale for ratings of morning alertness varied from "very alert" to "very drowsy".

Analysis of data. Results from the performance tasks were analyzed using repeated measures analysis of variance. Where appropriate, paired comparisons were subsequently undertaken using correlated t-tests. For the large print letter cancellation task, and for the Gibson spiral maze, the analyses of variance were run with two trial factors: treatment (lormetazepam; nitrazepam; and placebo); and test session (session 1 after the first dose and session 2 after the seventh dose). For the reciprocal tapping task data the analyses of variance contained a further trial factor: target size (6cm; 4cm; 3cm and 2cm). For both subjective variables, the average weekly rating for each Drug/Placebo week (Diagram 9:1) was calculated for each subject. The mean weekly ratings for each of three drug conditions were then compared using Friedman's non-parametric analysis of variance.

Results

Throughout this and the following section, the four target sizes on the reciprocal tapping task will be considered as four "target conditions".

None of the test measurements from the Gibson spiral maze (Tables 9:1, 9:2 and 9:3) or from the large print letter cancellation task (Tables 9:4, 9:5 and 9:6) showed significant main effects of, or significant interaction effects with, drug treatment. For the reciprocal tapping task, total contacts showed no significant main effect of, and no significant interaction effect with drug treatment (Table 9:7). Analysis of percent errors, however, while showing no significant main effect of drug, did show two significant interaction effects.

1. Drug treatment x session ($F = 8.26$; $df = 2, 22$; $p<0.005$); and
2. Drug treatment x target x session ($F = 2.85$; $df = 6, 66$; $p<0.05$); see Table 9:8.

The two-way interaction (drug treatment x session) is shown in Figure 9:1. T-tests calculated between the treatment means following a single dose showed that while neither lormetazepam nor nitrazepam error scores differed significantly from placebo, performance associated with nitrazepam was significantly superior to that associated with lormetazepam ($t = 2.90$, $df = 11$, $p<0.05$; Table 9:13). After seven consecutive doses, however, performance following nitrazepam was significantly impaired relative to both

lormetazepam ($t = 2.54$; $df = 11$; $p<0.05$), and placebo ($t = 3.00$; $df = 11$, $p<0.01$).

The significant three-way interaction (drug treatment x target x session) was further analyzed by repeating the analyses of variance for each target size independently (i.e. one ANOVA for the 2cm target condition, one for the 3cm target condition, etc.). The results from these four analyses of variance are shown in Tables 9:9, 9:10, 9:11 and 9:12. The 6cm and 4cm targets showed no significant main effect of, and no significant interaction effects with the drug factor. Both the 3cm and the 2cm target conditions, however, showed significant interactions between drug and test session ($F = 12.43$; $df = 2, 22$; $p<0.001$, for the 3cm targets; and $F = 3.76$; $df = 2, 22$; $p<0.05$, for the 2cm targets). These interactions are shown in Figures 9:2 and 9:3 respectively.

For the 3cm target condition, paired comparisons between the treatments showed that, after single doses, error scores associated with the two active drugs did not differ significantly from placebo values. At this time of testing significant differences were present between the drug conditions, performance under the nitrazepam condition being significantly superior to that under lormetazepam ($t = 4.03$, $df = 11$, $p<0.01$). After seven consecutive doses, however, performance under nitrazepam was significantly worse than that associated with both placebo ($t = 3.46$; $df = 11$, $p<0.01$), and lormetazepam ($t = 3.32$; $df = 11$; $p<0.01$). For the 2cm targets, there were no significant

TABLE 9:1. Analysis of variance of Gibson spiral maze: (Time)

	Sum of Squares	df	Mean Square	F	p
Mean	534129.981	1	534129.981	129.67	0.0000
Error	45310.527	11	4119.138		
Drug	809.249	2	404.624	2.28	0.125
Error	3904.362	22	177.471		
Session	709.388	1	709.388	3.28	0.097
Error	2377.341	11	216.121		
D x S	551.442	2	275.721	1.13	0.342
Error	5385.117	22	244.778		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:2. Analysis of variance of Gibson spiral maze: (Error)

	Sum of Squares	df	Mean Square	F	p
Mean	59627.555	1	59627.555	35.40	0.001
Error	18527.111	11	1684.282		
Drug	62.861	2	31.430	0.21	0.808
Error	3219.472	22	146.339		
Session	227.555	1	227.555	5.34	0.041
Error	468.444	11	42.585		
D x S	200.861	2	100.430	1.72	0.201
Error	1282.138	22	58.279		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:3. Analysis of variance of Gibson spiral maze: (Log Error)

	Sum of Squares	df	Mean Square	F	p
Mean	981638.571	1	981638.571	203.41	0.000
Error	53085.325	11	4825.938		
Drug	1250.093	2	625.046	0.83	0.447
Error	16503.782	22	750.172		
Session	839.953	1	839.953	1.67	0.223
Error	5545.177	11	504.107		
D x S	434.730	2	217.365	0.25	0.783
Error	19381.740	22	880.988		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:4. Analysis of variance of letter cancellation task: ("e"s Hit)

	Sum of Squares	df	Mean Square	F	p
Mean	71820.500	1	71820.500	79.91	0.0000
Error	10271.833	11	933.80		
Drug	55.083	2	27.541	1.15	0.3348
Error	526.583	22	23.935		
Session	60.500	1	60.500	1.32	0.274
Error	503.823	11	45.803		
D x S	2.583	2	1.291	0.09	0.911
Error	305.083	22	13.867		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:5. Analysis of variance of letter cancellation: ("e"s missed)

	Sum of Squares	df	Mean Square	F	p
Mean	21562.722	1	21562.722	41.15	0.0000
Error	5764.277	11	524.025		
Drug	134.694	2	67.347	0.47	0.633
Error	3180.305	22	144.559		
Session	12.500	1	12.500	0.18	0.675
Error	745.166	11	67.742		
D x S	166.583	2	83.291	1.17	0.329
Error	1567.750	22	71.261		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:6. Analysis of variance of letter cancellation task: (percent "e"s hit)

	Sum of Squares	df	Mean Square	F	p
Mean	309645.090	1	309645.090	180.74	0.000
Error	18845.361	11	1713.214		
Drug	110.357	2	55.178	0.41	0.66
Error	2942.758	22	133.761		
Session	36.551	1	36.551	0.32	0.584
Error	1265.520	11	115.047		
D x S	193.676	2	96.838	1.23	0.312
Error	1734.181	22	78.826		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:7. Analysis of variance of reciprocal tapping task: (total contacts)

	Sum of Squares	df	Mean Square	F	p
Mean	1004003.542	1	1004003.542	374.84	0.0000
Error	29463.572	11	2678.506		
Drug	437.137	2	218.568	1.29	0.295
Error	3732.529	22	169.660		
Session	4.882	1	4.882	0.06	0.80
Error	836.440	11	76.040		
D x S	295.192	2	147.596	1.20	0.320
Error	2707.640	22	123.074		
Target	4397.002	3	1465.667	37.07	0.0000
Error	1304.674	33	39.535		
D x T	70.411	6	11.735	0.80	0.571
Error	964.255	66	14.609		
S x T	70.134	3	23.378	1.01	0.399
Error	761.334	33	23.070		
D x S x T	101.383	6	16.897	0.93	0.477
Error		66			

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

Target = 2cm; 3cm; 4cm and 6cm target sizes

TABLE 9:8. Analysis of variance of reciprocal tapping task: (percent errors)

	Sum of Squares	df	Mean Square	F	p
Mean	28384.299	1	28384.299	72.09	0.000
Error	4331.329	11	393.757		
Drug	148.536	2	74.268	1.14	0.33
Error	1436.901	22			
Session	162.119	1	162.119	4.17	0.065
Error	427.245	11	38.840		
D x S	556.164	2	278.082	8.26	0.002
Error	740.798	22	33.672		
Target	601.604	3	4200.534	73.88	0.0000
Error	1876.371	33	56.859		
D x T	234.453	6	39.075	1.29	0.273
Error	1997.412	66	30.263		
S x T	20.430	3	6.81	0.41	0.749
Error	552.935	33	16.755		
D x S x T	288.703	6	48.117	2.85	0.015
Error	1114.297	66	16.883		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

Target = 2cm; 3cm; 4cm and 6cm target sizes

TABLE 9:9. Analysis of variance of reciprocal tapping task: (2cm Target Errors)

	Sum of Squares	df	Mean Square	F	p
Mean	30696.209	1	30696.209	127.10	0.0000
Error	2656.601	11	241.509		
Drug	367.112	2	183.556	1.66	0.213
Error	2435.210	22	110.691		
Session	76.322	1	76.322	1.50	0.246
Error	560.168	11	50.924		
D x S	404.613	2	202.306	4.89	0.0175
Error					

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:10. Analysis of variance of reciprocal tapping task: (3cm Target Errors)

	Sum of Squares	df	Mean Square	F	p
Mean	6837.869	1	6837.869	57.97	0.0000
Error	1297.612	11	117.964		
Drug	2.096	2	1.048	0.05	0.948
Error	433.773	22	19.716		
Session	66.393	1	66.393	3.29	0.097
Error	222.150	11	20.195		
D x S	346.673	2	173.336	12.43	0.0002
Error	306.902	22	13.950		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:11. Analysis of variance of reciprocal tapping task: (4cm Target Errors)

	Sum of Squares	df	Mean Square	F	p
Mean	2736.396	1	2736.396	19.66	0.0010
Error	1530.878	11	139.170		
Drug	6.115	2	3.057	0.23	0.798
Error	296.326	22	13.469		
Session	30.458	1	30.458	2.79	0.122
Error	119.932	11	10.903		
D x S	63.768	2	31.884	2.17	0.138
Error	323.325	22	14.696		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

TABLE 9:12. Analysis of variance of reciprocal tapping task: (6cm Target Errors)

	Sum of Squares	df	Mean Square	F	p
Mean	715.428	1	715.428	10.89	0.007
Error	722.609	11	65.691		
Drug	7.665	2	3.832	0.31	0.734
Error	269.003	22	12.227		
Session	9.374	1	9.374	1.32	0.274
Error	77.929	11	7.084		
D x S	29.812	2	14.906	1.04	0.370
Error	314.830	22	14.310		

Drug = lormetazepam 1 mg; nitrazepam 5 mg; placebo

Session = test session 1 (after a single dose) and
test session 2 (after seven consecutive doses)

EFFECTS OF NITRAZEPAM, LORMETAZEPAM, AND PLACEBO ON THE ACCURACY OF RECIPROCAL TAPPING IN 12 ELDERLY SUBJECTS (MEAN AGE = 81.4 YEARS)

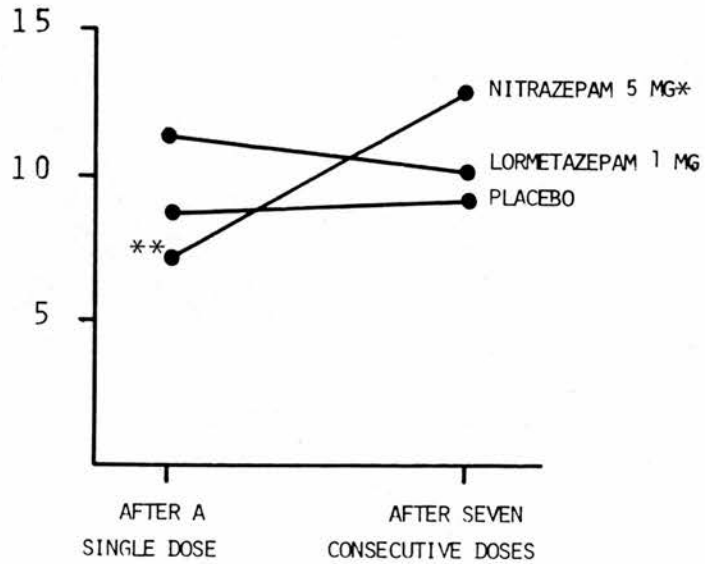


Figure 9:1
(overall accuracy)

* DIFFERS FROM PLACEBO: P = 0.012
** differs significantly from lormetazepam p = 0.014

EFFECTS OF NITRAZEPAM, LORMETAZEPAM, AND PLACEBO ON THE ACCURACY OF RECIPROCAL TAPPING: 3 CM TARGETS

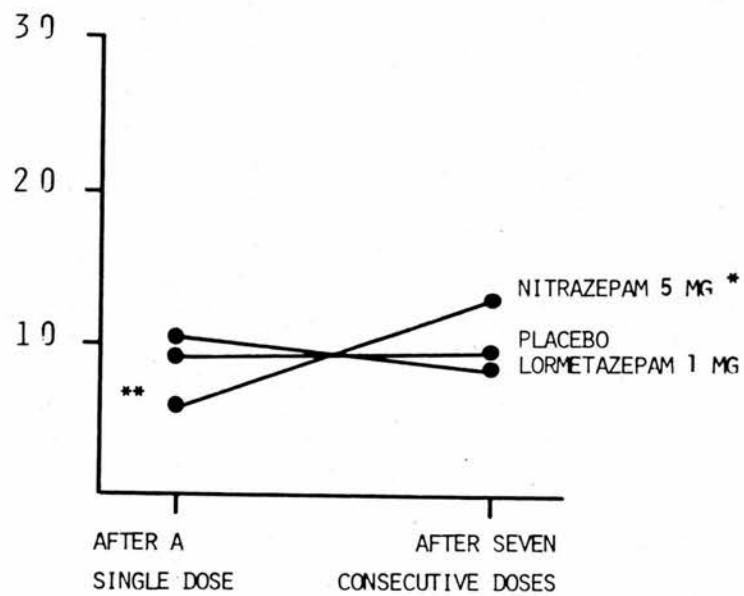


Figure 9:2

* DIFFERS SIGNIFICANTLY FROM PLACEBO: P = 0.005

** DIFFERS SIGNIFICANTLY FROM LORMETAZEPAM: P = 0.002

EFFECTS OF NITRAZEPAM, LORMETAZEPAM, AND PLACEBO ON THE ACCURACY OF RECIPROCAL TAPPING: 2 CM TARGETS

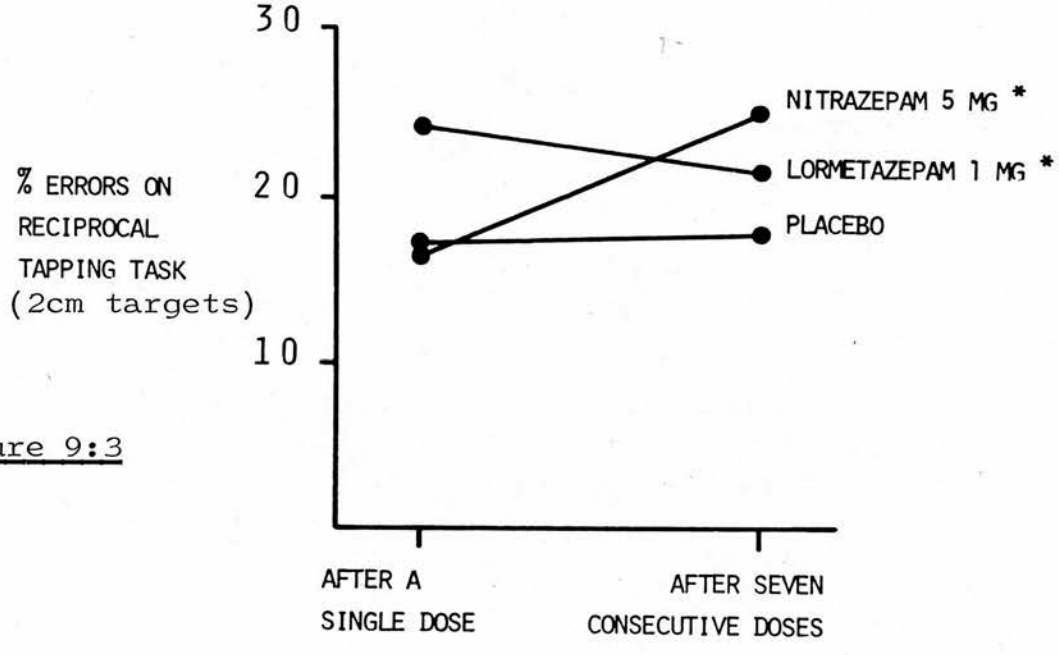


Figure 9:3

* DIFFERS SIGNIFICANTLY FROM PLACEBO: P 0.05

TABLE 9:13. Reciprocal tapping task (mean percent errors): Values of t (correlated) for paired comparisons

After a single dose

Treatment (mean; SD)	v	Treatment (mean; SD)	t-value	p *
lormetazepam 1 mg (11.34; 4.87)		placebo (8.72; 4.30)	1.45	0.175
nitrazepam 5 mg (7.48; 4.65)		placebo	0.63	0.543
lormetazepam 1mg		nitrazepam 5 mg	2.90	0.014

After seven consecutive doses

lormetazepam 1mg (10.05; 5.19)		placebo (9.22; 4.12)	0.87	0.402
nitrazepam 5 mg (12.77; 7.06)		placebo	3.00	0.012
lormetazepam 1 mg		nitrazepam 5 mg	2.54	0.028

TABLE 9:14. Reciprocal tapping task (percent errors: 3cm target): Values of t (correlated) for paired comparisons

After a single dose

Treatment (mean; SD)	v	Treatment (mean; SD)	t-value	p *
lormetazepam 1 mg (11.11; 5.36)		placebo (9.24; 5.47)	0.90	0.387
nitrazepam 5 mg (6.01; 3.39)		placebo	1.63	0.131
lormetazepam 1 mg		nitrazepam 5 mg	4.03	0.002

After seven consecutive doses

lormetazepam 1 mg (8.45; 6.42)		placebo (9.80; 5.84)	0.78	0.453
nitrazepam 5 mg (13.86; 7.75)		placebo	3.46	0.005
lormetazepam 1 mg		nitrazepam 5 mg	3.32	0.007

* Two-tailed significance values throughout

TABLE 9:15. Reciprocal tapping task (percent errors: 2cm targets)
Values of t (correlated) for paired comparisons

After a single dose

Treatment (mean; SD)	v	Treatment (mean; SD)	t-value	p *
lormetazepam 1 mg (24.48; 10.40)		placebo (17.31; 8.81)	2.01	0.069
nitrazepam 5 mg (17.06; 11.38)		placebo	0.05	0.960
lormetazepam 1 mg		nitrazepam 5 mg	1.75	0.109

After seven consecutive doses

lormetazepam 1 mg (21.59; 7.77)		placebo (17.93; 8.31)	2.50	0.03
nitrazepam 5 mg (25.51; 12.32)		placebo	2.32	0.041
lormetazepam 1 mg		nitrazepam 5 mg	1.38	0.195

* Two-tailed significance values throughout

differences between either of the drug treatments and placebo after a single dose, but significantly more errors were made following seven consecutive doses of both nitrazepam ($t = 2.32$; $df = 11$, $p<0.05$) and lormetazepam ($t = 2.50$; $df = 11$; $p<0.05$). The results of paired comparisons (t-values) for the treatment means illustrated in Figures 9:1, 9:2 and 9:3, are shown in Tables 9:13, 9:14 and 9:15 respectively.

For both subjective variables, Friedman's analysis of variance showed no effect of drug condition on either sleep quality (chi-square = 0.292; df = 2; p = 0.864) or morning alertness (chi-square = 3.167; df = 2; p = 0.205).

Discussion

The results from each test will be discussed in turn. Conclusions are presented at the end of this section.

Reciprocal Tapping Task.

Neither drug significantly affected speed of performance (as measured by mean total contacts) on the reciprocal tapping task. Nitrazepam 5.0mg, however, was associated with an overall impairment of accuracy consistent with drug accumulation, with mean errors increasing significantly between the first and seventh consecutive doses (Figure 9:1). This decrement was not independent of the differing demands of task. Figures 9:2 and 9:3

show similar patterns of nitrazepam-associated impairment for the 3cm and 2cm target conditions respectively; again, errors increased significantly between the first and seventh consecutive doses. Thus, as the target sizes decreased, task complexity increased, and errors became more probable following seven consecutive doses of nitrazepam 5.0mg. These results accord with the data presented in the previous chapter.

A very different pattern of effects is shown for lormetazepam 1.0mg. For this shorter acting drug, mean errors tended to decrease between the first and seventh doses. At low (6cm and 4cm targets) and intermediate (3cm targets) levels of task complexity, performance following lormetazepam did not differ significantly from placebo. At the highest level of task complexity (2cm targets), errors did increase following seven consecutive doses (Figure 9:3). [From Figure 9:3 it can be seen that while the mean error score following single dose lormetazepam was greater than that following seven consecutive doses, only the latter values differed significantly from placebo. From the standard deviations shown in Table 9:15, however, it is evident that the scatter of data was greater following the single dose.] In young adult (Nicholson and Stone, 1982) and middle-aged (Oswald et al. (1979) subjects lormetazepam in 1.0mg doses has been reported to be devoid of measurable residual effects on daytime performance. The presence of impaired tapping accuracy in the present study, therefore, emphasizes the increased vulnerability of elderly individuals to the detrimental residual effects of hypnotic drugs.

The performance decrements on this task associated with repeated doses of nitrazepam 0.5mg are both consistent, and profound. In terms of overall accuracy (Figure 9:1), performance following seven repeated doses of nitrazepam was significantly inferior to that following both placebo and lormetazepam.

An interesting feature of these data is the apparent facilitation of accuracy following single dose nitrazepam 5.0mg, which achieved significance relative to lormetazepam in mean total errors (Figure 9:1) and in the the 3cm target condition (Figure 9:2). This finding is consonant with the suggestion made in Chapter 5 that, as test performance efficiency in the elderly appears to be particularly vulnerable to stress factors engendered by the testing process (Rabbit, 1982), residual anxiolytic activity may enhance performance. Should this have been the case, it is clear that any such advantage is rapidly negated by drug accumulation.

Gibson Spiral Maze

None of the measurements derived from the Gibson spiral maze showed significant differences between drug and placebo conditions (Tables 9:1, 9:2, and 9:3). Salem et al. (1982) report significant slowing on this task in elderly females 11h after single dose nitrazepam 10mg; in the same experiment, no effect was reported for elderly males. Given that the present subjects were predominantly female, these results suggest a dose-dependent

relationship between nitrazepam and the occurrence of residual effects in the elderly. Such a relationship has already been noted in healthy young adult subjects (e.g. Malpas et al. 1970; Bond and Lader, 1972).

Letter Cancellation

None of the measurements derived from the letter cancellation task distinguished between drug and placebo conditions (Tables 9:4, 9:5, and 9:6). Nayal et al. (1978) used a version of this task in which elderly subjects were required to delete all the letter "e"s from a complete page of prose as quickly as possible. Measuring both the speed (in seconds) and the number of "e"s deleted, these researchers found the test to be similarly insensitive in distinguishing between the residual effects of single dose nitrazepam 5mg and chlormethiazole 384mg (base), but suggested that the sensitivity of the task might be improved if the procedure was paced (i.e. conducted over a fixed period of time). Just such a modification to the cancellation task was employed by Briggs et al. (1980) in their comparison of the residual effects of chlormethiazole 384mg (base) and temazepam 20mg in young and elderly subjects. In this case, performance timed over two minutes on the task did not distinguish between the drug and placebo conditions. More recently, Cook et al. (1983), using an un-paced version of the same task, found a significant slowing of performance following single dose temazepam 20mg, and multiple dose nitrazepam 5mg. However, these authors also report slowing of performance following repeated doses of

placebo treatments, and comment that, on the cancellation task, some subjects "tended to lose interest with repeated testing". Consequently, Cook et al. (1983) suggest that the test would yield more consistent results if administered over a two minute period. Combining these previous findings from, and equivocal comments regarding this test with the results from the present study, it cannot be concluded that the letter cancellation task is a particularly reliable, stable or sensitive measure of residual effects in the elderly following low-dose, or short-acting hypnotic drugs.

Subjective Ratings

Neither of the subjective ratings proved to be sensitive in distinguishing between drug and placebo conditions. As regards the subject's own ratings of sleep quality, these showed extreme daily variations which were more suggestive of dichotomous (i.e. either satisfaction or disatisfaction with) rather than analogue judgements of the previous night's sleep. On the other hand, staff ratings of alertness were conservative throughout, reflecting the tendency, already seen in the previous experiment, for staff to favour the "no change" position on the scale. The efficiency of the subjective rating as a research tool is entirely dependent on the comprehension and motivation of those completing the scales. In the present circumstances, then, it must be concluded that these negative results, particularly as regards sleep quality, do not challenge previously reported findings. Oswald et al (1979), for example, report that middle aged subjects

consistently reported their sleep as improved following lormetazepam 1mg and 2.5mg, a finding in agreement with EEG recordings from the same study.

Conclusions

The present study provides clear evidence that, relative to the longer acting nitrazepam, repeated doses of lormetazepam 1.0mg are less likely to be associated with profound performance decrements in the elderly. Repeated doses of nitrazepam produced a generalized and significant reduction of efficiency on the reciprocal tapping task relative to both placebo and lormetazepam 1.0mg (Figure 9:1). Conversely, the detrimental effects of lormetazepam were seen only at the highest level of task complexity (Figure 9:3). The overall pattern of performance following single and repeated doses of nitrazepam was consistent with drug accumulation, a finding in agreement with the results of Experiment 2 and with the recently reported results of Cook et al. (1983). In general, such was not the case following lormetazepam. That neither drug significantly affected the speed of performance on the reciprocal tapping task again suggests that such decrements in efficiency are related to impaired judgement of accuracy as described in Chapter 8. Both drugs, in the doses used in the present study, have been shown to be effective hypnotics in older subjects in sleep laboratory investigations (Adam et al. 1976 for nitrazepam 5.0mg; Oswald et al. 1979 for lormetazepam 1.0mg). It is therefore reasonable to conclude that, for the

short-term treatment of disturbed sleep in the elderly, a shorter acting hypnotic drug is clinically and psychologically preferable. Caution is, nevertheless, appropriate here. On the reciprocal tapping task detrimental residual activity was apparent following the seventh consecutive dose of lormetazepam at the highest level of task complexity (2cm targets).

The pattern of performance decrements shown for nitrazepam 5.0mg in the previous chapter is adequately replicated in the present study. The testing procedure used in these studies, therefore, offers a robust means for evaluating the residual effects of further hypnotics in this age group. As regards the testing procedures and the experimental methodology, one further point deserves to be emphasized. While the previous experiment (Chapter 8) was conducted in a purpose-built performance laboratory, the present study was conducted in the homes of the participating subjects. Nicholson and Stone (1982) have recently criticised multiple dose experimental evaluations of hypnotic drugs, suggesting that such studies: 1) do not guarantee compliance in the taking of experimental drugs; 2) cannot provide adequate supervision over the "circumstances and behaviour of subjects" in the period immediately preceding performance testing, and therefore 3) are more likely to produce variable and unreliable data. Nicholson and Stone (1982) contrast these points with the experimental control possible in single-dose studies where subjects are constantly supervised by the experimenter in the laboratory.

None of these criticisms, however, gains support from the present study. Compliance, for example, was guaranteed by the standardized drug administration procedures of the residential homes. While control over the "circumstances and behaviour of subjects" was, indeed, not possible between testing sessions, it can be seen from the results presented here that the data are far from variable. Table 9:13 for example shows that, under placebo conditions, mean total errors on the reciprocal tapping task differed by less than one percentage point between the first and second testing sessions (a period of one week). As regards variability, the standard deviations of these mean values differ by less than 0.2 of a percentage point (Table 9:13). Thus, the present study offers, not only a reliable test procedure for evaluating residual drug effects in the elderly, but also offers a reliable alternative to costly and, in this age group, inconvenient attendances at performance laboratories. Through the use of efficient subject selection procedures (e.g. the Clifton Assessment Procedures for the Elderly), appropriately selected and validated tests (e.g. the reciprocal tapping task), and strictly standardized performance testing procedures, it is clear that an effective degree of experimental control can be maintained outside the laboratory.

The demerits of the present study should not, however, be overlooked. The apparent insensitivity of the subjective ratings requires particular attention. In single dose laboratory studies with elderly subjects, visual analogue scales have proved sensitive in distinguishing nitrazepam 10mg (Castleden et al.

1977), chlormethiazole 384mg, and temazepam 20mg (Briggs et al. 1980) from placebo. The sensitivity of these instruments in multiple dose evaluations in the elderly has not been established. While nurse ratings have been favoured in multiple-dose hospital studies of hypnotics in the elderly (e.g. Linnoila and Viukari, 1976; Viukari et al. 1978), sleep questionnaires have been used in community samples. Reeves (1977), for example, in a 28 day study of the hypnotic efficacy of triazolam 0.25mg in geriatric outpatients (mean age = 68.6y) successfully used a forced-choice questionnaire to assess sleep quality, morning alertness, and side-effects. Relative to the scales used in the present study, one possible advantage of Reeves' (1977) procedures is that forced choice responses are cued (e.g. "did you sleep: very well?; well?; poorly?; very poorly?"). In very elderly subjects, many of whom have low expectations of sleep satisfaction, such cues may in turn prompt a more thoughtful response. Certainly, the need exists here for future research and development. It is relevant to point out, nevertheless, that even in younger, motivated and experienced subjects (such as the participants in Experiment 1) visual analogue ratings are not flawless, and may reflect demand characteristics and response bias. The daily ratings of sleep quality shown for Experiment 1 (Chapter 4) show a clear tendency for subjects to rate their sleep as improved under placebo conditions (Figure 4:1).

Chapter 10

A synopsis of the studies presented in this thesis, and a summary of conclusions.

Before discussing the implications of the studies reported here, it would be useful to reiterate the overall aims of this thesis and present, in brief, the rationale and a summary of findings for each study. This chapter will also allow an opportunity to present relevant research findings which have been reported since the work here was undertaken.

The overall aim of the thesis, as described in chapter 1, was to identify, and respond to areas of the drug-performance literature where clinically relevant information concerning the influence of ageing was particularly lacking. Chapters 1 and 2 showed that, while age has long been regarded as a relevant subject variable in the assessment of the residual effects of hypnotic drugs, it has nevertheless received little experimental attention. Chapter 2 further showed that the consensus of opinion among researchers suggested that residual effects on behaviour are less likely to accompany the use of short half-life hypnotic drugs. These two factors were brought together in Experiment 1 which examined the effects of repeated doses of two relatively short-acting hypnotics, triazolam and loprazolam, both within a group, and between sub-groups of middle aged individuals. The results provided no evidence of cumulative residual activity of either drug within the group, and no clear systematic differences

in overt performance between the early and late middle-aged sub-groups. Nevertheless, subjective ratings made by each subject throughout the study showed a significant increase in feelings of daytime anxiety following repeated doses of triazolam 0.5mg relative to the longer acting loprazolam. This latter finding has since been confirmed by Kales et al. (1973). These researchers compared self-reports of daytime anxiety following repeated doses of two short-acting (triazolam 0.5mg and midazolam 20mg) with those following repeated doses of two long acting hypnotics (flurazepam 30mg and quazepam 30mg), and report a relative, though significant increase in anxiety after 2 weeks administration of triazolam, and after 1 week of midazolam. In agreement with the conclusions presented in Chapter 4, Kales et al. (1983) attribute these findings to daytime withdrawal phenomena.

Certain characteristics of the data from Experiment 1 indicated that, in general, these middle-aged subjects may have efficiently compensated for residual drug effects. Epidemiological, clinical, and experimental evidence reviewed in Chapter 5, however, suggested that the behavioural integrity of elderly individuals (defined as the age group 65y+) is relatively more vulnerable to the residual effects of hypnotic drugs. It was also noted that experimental interest in this age group was particularly lacking. Furthermore, in several of the studies reporting the presence or absence of residual drug effects in the elderly, it was clear that theoretical issues highly relevant to the testing of elderly individuals had been ignored. While Chapter 5 emphasized the increased risk of untoward behavioural

reactions to hypnotics in the elderly, Chapter 6 analyzed and emphasized the greater probability of hypnotic drugs being prescribed for and used by this age group. The temporal trends observed in this review showed that sleeping drug use, and the consequent risk of behavioural impairment, has not decreased in relative or absolute terms over the past 20y. The drug-use literature was not sufficiently specific to allow for the identification, for subsequent experimental analyses, of typical drugs and typical dosages in current use among the elderly.

The two surveys of hypnotic drug usage in residential homes for the elderly were conducted both for their intrinsic clinical value as feedback for practitioners, and to guide clinically relevant experimental research. Both surveys showed that extensive use was not being made of short-acting hypnotic drugs, despite the theoretical advantages associated with these products. On the contrary, the long-acting hypnotic nitrazepam was most used. A similar finding in the United States has since been reported by Stewart et al. (1982). This study examined the prescription hypnotics of 210 elderly individuals in a retirement community in Florida, and found that almost 75% of all prescriptions were for the long-acting drug flurazepam. From evidence reviewed in Chapter 5 it was concluded that reduced mental and physical health status in the elderly was associated with an increased susceptibiltiy to the adverse behavioural effects of hypnotic drugs. The survey data were therefore examined for evidence of discrimination in the prescribing of drugs for impaired and non-impaired groups of residents. From

these analyses it was apparent that, while reduced health status was associated with a reduced probability of receiving hypnotic drugs within the homes, usage in the impaired groups was equal to, or greater than that found in many community surveys. These data, therefore, indicated a relative increase in usage in the non-impaired group rather than a relative decrease in usage among the impaired. Again, it should be noted that examining the characteristics of prescribing practices within institutional settings is not without broad clinical relevance. Recent estimates suggest that, at any one time, almost half a million elderly individuals in the UK are in some form of institutional care, which includes 131,000 in local authority homes (Department of Health and Social Security, 1980), 70,000 in private and voluntary homes (DHSS, 1980), and 31,000 in voluntary hospitals and private nursing homes (DHSS, 1980). A further 220,000 elderly individuals are estimated to occupy National Health Servive beds (DHSS, 1980; Chaplin, 1981). Insofar as they affect the prescribing of hypnotic drugs, it would not be unreasonable to assume that the relationships which exist between carers, the elderly, and the prescribing physicians, share some common features within these different institutions.

Assumptions concerning the safety of low dose nitrazepam in the elderly, apparent from the survey data presented in Chapter 7, were tested in Experiment 2 (Chapter 8). The results from this study conformed with the predictions made in Chapter 2 regarding long acting hypnotics. The performance deficit seen in the elderly subjects was consistent with drug accumulation over the

eight days of continuous usage. To further assess the prediction that, in elderly individuals in particular, significant residual effects are less likely to accompany the use of short-acting hypnotics, Experiment 3 (Chapter 9) compared the effects of multiple dose nitrazepam 5mg with those of the shorter acting lormetazepam 1mg. While nitrazepam 5mg again produced a generalized and significant reduction in performance efficiency, impairement associated with lormetazepam 1mg was specific to high levels of task complexity. Comparisons of the behavioural effects of long and shorter acting hypnotics in hospitalized elderly groups have subsequently shown similar relative differences (Murphy et al. 1982; Cook et al. 1983). It was also proposed in Chapter 5 that, on the basis of previous experimental results, interactions between the speed and accuracy of performance may be sensitive and reliable indicants of residual drug effects in the elderly. The results obtained in Experiments 2 and 3 supported this proposal.

This thesis has presented two distinct experimental approaches to the evaluation of the behavioural consequences of hypnotic drug use in older age groups. Experiment 1 characterizes the first approach in which relatively new hypnotic products are intensively investigated using subjects of an age representative of the drug's target population. Such an approach not only produces information of immediate clinical relevance, but also generates a substantial data-base that can be exploited in subsequent research. Experiments 2 and 3, on the other hand, address specific issues which emanate from the currently available

experimental and drug-use literature. Common to all three experiments, however, is the assumption that drug effects on psychological tasks provide a relevant and meaningful index of a drug's influence on "in vivo" behaviour. This premise will briefly be considered before the conclusions from this thesis are presented.

It is recognized here that the use of psychological testing procedures is not the only means by which the behavioural effects of hypnotic drugs may be evaluated. In recent years, a growing interest has developed in the assessment of drug effects on quite specific skills, particularly motor car driving. Evaluations of both simulated (e.g. Linnoila et al. 1974) and actual (e.g. Betts et al. 1972) car driving ability indicate that measurable impairment of this integrated skill may follow the use of various sedative and hypnotic drugs. When contrasted with the somewhat more esoteric data derived from laboratory performance tasks, the results from such studies certainly appear to be more immediately applicable to "real life" situations. It is realistic to enquire, therefore, with what degree of certainty can results be extrapolated from psychological test procedures?

This question can be approached from several different directions. In the case of car driving, for example, correlations may be sought between performance on psychological tasks and actual driving abilty. Such an approach is not without its methodological problems. Clayton (1976), for example, observes little relationship between a given individual's efficiency on

laboratory performance tasks, and that individual's traffic accident and violation rate, but points out that the lack of such a relationship "is unsurprising if accidents are regarded, not as a homogeneous body of events, but rather a collection of events with widely different causative processes whose sole common characteristic is the resultant collision". More recently, however, Hindmarch (1979) has reported data from a study in which subjects were tested on laboratory measures of critical flicker fusion threshold and choice reaction time and actual car driving ability following single doses of the benzodiazepine lorazepam. Hindmarch (1979) concludes that "The impairment of performance shown in the laboratory tests following the administration of a 1,4 derivative, lorazepam, has been mirrored in the reduced performance on actual car driving tests of brake reaction, steering, width estimation, parking, and garaging". Such data are in accord with the findings of Skegg et al. (1979) who report an association between serious road traffic accidents in five patients, and the use in each case of benzodiazepine minor tranquillizers.

Concern for and comparisons with undoubtedly useful laboratory-simulated or actual "real life" skills tends, however, to detract from the merits of psychological assessment in general. Fundamental to the notion of assessment, whether of perceptual-motor or cognitive skills, is the concept of pervasive psychological characteristics which mediate efficient performance. If laboratory studies reveal impairment on tests of say vigilance, then it is reasonable to extrapolate these findings

to "real" tasks which require, for their efficient execution, high levels of sustained attention. Such extrapolations are reasonable, however, only if the characteristics of performance measured possess an acceptable degree of construct validity, i.e. the degree to which the dependent variable (for example, auditory vigilance performance) is really measuring that with which we are concerned (the ability to sustain attention). In the experiments reported here, considerable emphasis has been placed on the constructs of vigilance (the auditory vigilance task), and information processing ability (the Crossman card-sorting task, the reciprocal tapping task). The validity of these constructs is both established (e.g. Mackworth, 1970; Welford, 1980) and widely recognized. Thus, as regards car driving efficiency, Clayton (1976) concludes that "drugs which have the potential for affecting attention or the speed of performance may be of particular danger in actual driving", and "if the tasks are measuring a reduced rate of information processing as a result of drug ingestion, then a translation of the effect to the driving situation may be expected". With particular reference to the elderly, a large proportion of whom do not drive, extrapolations to the driving situation are, at present, of limited relevance. Hypnotic drugs associated with daytime performance decrements in this age group do, nevertheless, represent a real threat to their quality of life.

Conclusions

On the basis of the evidence reviewed, it was suggested in

Chapter 5 that the residual effects of hypnotic drugs may amplify normal or abnormal ageing processes. An extreme example of this would be the hypnotic drug induced "pseudodementias" described by Evans and Jarvis (1972) and by Rudd (1972). In Experiments 2 and 3, the performance decrements following nitrazepam 5mg and, to a lesser extent, lormetazepam 1mg were characterized by a reduction in accuracy, but not speed. These results suggested a specific impairment of the processes mediating judgement, rather than a non-specific consequence of general sedation. Indirect support for this conclusion is provided by data reported by Kendrick and Moyes (1979) concerning the influence of anxiolytic and antidepressant drugs on sub-test performance in a diagnostic battery (the Revised Kendrick Battery). It was found that continued drug therapy with barbiturate hypnotics or tricyclic antidepressants was, in a significant number of patients, associated with a test profile in depressed groups similar to that in demented groups, a profile described by these authors as a reversible "drug-induced 'pseudodementia'". While the specific concern of the experiments reported here has been the integrity of performance following hypnotic drugs, these characteristics of the performance deficits observed, and their relationship to the ageing process, provide a basis for collateral and relevant future research.

The evidence reviewed in Chapter 5 further suggested that elderly individuals with existing cognitive impairments due to, say, dementia (Linnoila and Viukari. 1976; Viukari et al. 1978) may be more susceptible to the adverse behavioural effects of hypnotic drugs. It is, therefore, relevant to note a recently

published article which comes to exactly the opposite conclusions, that is, that the demented elderly are less sensitive to the residual effects of hypnotic drugs. Mead and Castleden (1982) report a balanced, within-subjects comparison of the effects of single- dose chlormethiazole 384mg, temazepam 20mg, and placebo in 11 elderly demented hospital inpatients. Eleven hours after each treatment subjects were tested on: 1) standardized questions to assess mental status; a two-minute letter "e" cancellation task; and a "sway" test using an ataxiameter. No difference was found between drug and placebo values for each test, and Mead and Castleden (1982) conclude "The lack of impaired psychomotor performance lends no support to the contention that confused patients are more sensitive to sedative drugs". The validity of this conclusion demands scrutiny. Of the two tests measuring psychomotor efficiency (sway and letter cancellation) the authors report that "The (sway) test was abandoned because of inability of most of the patients to cooperate". For the remaining letter cancellation task, data were collected from only 7 patients, of the remaining 4 "One was unrousable the next morning, one had lost her glasses and two could not see the print" (op. cit.). It can be assumed from these latter comments that no pre-experiment practice sessions were conducted. Even for the 7 patients who did complete the cancellation task, the authors remark that "poor vision hampered attainment". Given these circumstances, then, the available test results from this study hardly represent sensitive indicants of psychomotor ability. Other features of this study deserve attention. The dose of chlormethiazole is described as "(edisylate) 384mg". If this was the case, then a

dose of untypically low potency was used. More likely, however, the authors used (base) 384mg (equivalent to edisylate 500mg). [Indeed, a preparation of chlormethiazole (edisylate) 384mg is not manufactured]. As mean plasma concentrations for both drugs were considerably higher than those reported in a previous experiment (Briggs et al. 1980), the authors concluded that the data reflect a relative decrease in sensitivity to hypnotics in the demented elderly. Considered in relation to the literature and the issues discussed in Chapter 5, this study does not represent a sufficiently rigorous test of the hypothesis that existing cognitive impairment exacerbates the detrimental effects of hypnotic drugs on performance in the elderly.

As pointed out in Chapter 6, four factors contribute to the probability of adverse behavioural reactions accompanying hypnotic drug use: 1) the pharmacological characteristics of the drug; 2) the dose of drug used; 3) the duration of usage; and 4) the age (and health status) of the recipient. The results from the present studies will be considered in relation to each of this factors, and also in relation to the broader issue of an hypnotic drug prescribing policy in older patients.

The present studies demonstrate that elimination half-life is a reliable predictor of daytime residual effects. However, some of the results clearly indicate that residual effects, i.e. those effects associated with persistent pharmacological activity, are not the only potential source of behavioural

disruption from hypnotic drugs. Problems of increased anxiety associated with repeated doses of the very short acting triazolam were identified in Experiment 1. It is also relevant to note that, in the elderly, the elimination half-life of the drug may not be the only pharmacokinetic feature predictive of behavioral side effects. The data of Witts (1979) show that, while seven repeated doses of chlormethiazole in elderly patients did not affect the elimination half-life of the drug, peak plasma concentrations increased considerably between the first and seventh consecutive doses. The authors concluded that multiple dosing results in increased bioavailabilty of chlormethiazole in elderly patients. The acute pharmacological response to a non-cumulative drug may, therefore, increase with repeated doses in elderly patients.

From the results presented in Experiments 2 and 3 it is clear that untoward behavioural effects are probably best avoided at the level of drug, rather than at the level of dose. The cumulative properties of nitrazepam were evident in both experiments, even though the dose used was low and, for this age group, recommended. Dose factors are, nevertheless, of importance even in non-cumulative compounds. It is possible that the relative increase in anxiety following triazolam usage in Experiment 1 was dose-dependent, and that such effects may be avoided by using lower dosages. Thus, these results indicate that the effects of hypnotics on daytime performance can be significantly controlled through the use of shorter acting drugs in the lowest dose compatible with hypnotic efficacy. Oswald (1983), has recently

suggested that an elimination half-life of 10h is probably optimal for hypnotic drugs. It should be remembered, however, that mean elimination half-lives estimated in younger age groups are not necessarily applicable to the elderly.

Clinical concern for the increasing use of prescription medicines with age, and the consequent risks of iatrogenic disorders, were noted in Chapter 7. The use of sedative-hypnotic drugs among the elderly has attracted, not only clinical, but also sociological and political concern (Dement, Miles et al. 1982; Green, 1982). It is appropriate, therefore, that the results reported here should finally be considered in the wider context of drug prescribing policies. In combination, the interrelated factors of age and the duration of hypnotic drug usage represent a particularly important issue in drug prescribing for the older patient.

The results from the experiments reported here clearly show that, in older subjects, prolonged hypnotic drug usage increases the probability of daytime behavioural disruptions. The relative increase in anxiety reported for triazolam 0.5mg in Experiment 1 reached significance only in the second and third weeks of administration. The reductions in overall efficiency reported for nitrazepam 5mg were significant only after eight (Experiment 2) and seven (Experiment 3) consecutive doses. Significant impairment associated with lormetazepam 1.0mg on the reciprocal tapping task (Experiment 3) was apparent only after seven consecutive doses. Thus, these experimental findings strongly

support the conclusions of the Committee on Safety of Medicines (1980), which recommended that the use of benzodiazepine therapy for insomnia in the elderly "be undertaken for short periods of time, and only after careful consideration". The results from Surveys 1 and 2, however, indicate that the long-term prescribing and use of hypnotic drugs among the elderly is not untypical, a finding reflected in several of the studies reviewed in Chapter 6. Clearly, then, there exists at present a discrepancy between policy and practice.

Dement et al. (1982) have recently pointed out that hypnotic drugs are of optimal value in the symptomatic relief of "transient situational insomnia". Such a diagnostic category, however, far from characterizes the sleep disturbances reported for ageing populations. Chapter 6 shows that dissatisfaction with sleep increases predictably with age. Dement, Miles et al. (1982), for example, comment that disturbed sleep "appears to be ubiquitous among the elderly". Thus, in a significant number of elderly individuals, dissatisfaction with sleep is neither transient nor situational but appears, rather, to be permanent and constitutional. Consequently, and despite recommendations to the contrary, the prolonged use of hypnotic drugs remains more likely among elderly individuals. A further question that needs to be addressed, therefore, is whether or not the prescribing of hypnotic drugs is, in general, an appropriate clinical response to complaints of sleep dissatisfaction in the elderly. Dement, Miles et al. (1982), for example, refer to the prescribing of hypnotics for the institutionalized healthy elderly as "an abomination".

It is apparent from the information considered in Chapter 6, however, that the processes mediating the prescribing of hypnotics in older patients are multi-factorial, a feature which pre-empts any attempt to produce a simplistic solution. Equally complex, however, are the effects of regularly taken psychotropic drugs on the ecology of human behaviour. While experimental research of the type reported here aims to assist in the decision to prescribe one drug or another, further research and action is needed to assist in a more fundamental clinical decision - that between prescribing something, and prescribing nothing.

Summary of Conclusions

1) Unlike longer acting compounds, hypnotic drugs in which the elimination half-life does not exceed 15h are not associated with progressive impairments of performance with repeated doses in early and late middle-aged subjects.

2) Hypnotic drugs in which the the elimination half-life is less than 4h can, with repeated doses, produce subjective feelings of increased anxiety in early and late middle-aged subjects, such reactions being attributable to daytime drug withdrawal.

3) Intensive experimental evaluations of residual effects on performance, using subjects of an age group representative of the drugs target population, should precede the introduction of any new hypnotic compound. Such evaluations should simulate the clinical use of hypnotic drugs.

4) Quantifying residual drug effects in the elderly presents special methodological problems which do not apply in younger age groups. Attention to such factors as the assessment of cognitive status of subjects, the inclusion of practice sessions, and the appropriateness of tests can result in both reliable, and sensitive measures of a drugs pharmacological effect in this age group.

5) In elderly subjects, repeated low-doses of cumulative hypnotic drugs can impair performance. Such impairment is not seen after single dose.

6) In elderly subjects, drugs in which the elimination half-life is less than 15h are less likely to impair performance than are long acting cumulative drugs, even when the latter are administered in low doses.

7) Hypnotic drug-induced performance decrements in the elderly appear to be characterized by reductions in the efficiency of behaviour in the absence of significant compensatory reductions in speed. Such decrements suggest that the subject may, therefore, be unaware of the deficit. This feature of the performance deficit has broad implications for the safety of indepedent elderly individuals.

8) The ability to compensate for the residual effects of

hypnotics may differentiate between middle-aged and elderly individuals. Performance curves suggestive of compensation were present in the data from middle-aged subjects.

9) Clinical and experimental evidence concerning the behavioural disadvantages of long acting, cumulative hypnotic drugs is not, at this time, reflected in the prevalence with which these drugs are prescribed and used. The prescribing patterns observed in an elderly population continue to show the widespread use of drugs and dosages contra-indicated for use in this age group. Incidence data are required to establish current prescribing preferences.

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The research described in this thesis was conducted by the author. In the co-operative studies (Experiment 1; Surveys 2 and 3) the author was the principal contributor.

Signed.....(Kevin Morgan)

Appendix 1:1 (over). The Digit Symbol Substitution Test

Appendix 1:1

EXPERIMENT:

Name:

Date:

Time:

Score: completed

errors

correct

CODING TASK

This is a task of coding symbols into their corresponding numbers. You are to code as many symbols as accurately as you can.

The symbols and their coding appear at the top of the first page and obviously, if you can remember them you will get more completed in the time allowed. It is not expected that you will get all the coding completed but **remember to work steadily and accurately.**

THE TIME FOR THIS TASK IS:

If you have any questions, ASK NOW.

Do not turn the page until you are told

Appendix 1:1

CODE:

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Appendix 1:1

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Appendix 2 Analysis of Variance Tables for the data summarized in Table 3:1.

For each table, the factors (source) are as follows:

Age (A) = older sub-group; younger sub-group.

Drug (D) = loprazolam 1.0mg; loprazolam 0.5mg; triazolam 0.5mg; placebo.

Week (W) = week 1 testing session; week 2 testing session; week 3 testing session.

Time (T) = 08.30 time of testing; 12.30 time of testing; 16.30 time of testing.

Appendix 2:1 Analysis of variance of Auditory Vigilance task data: percent correct detections over 1h

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	2542111.10005	1	2542111.10005	468.95	0.0000
	AGE	14610.07109	1	14610.07109	2.70	0.1317
1	ERROR	54208.90235	10	5420.89023		
	DRUG	1090.07482	3	363.35827	0.60	0.6228
	DA	313.19095	3	104.39698	0.17	0.9150
2	ERROR	18300.77281	30	610.02576		
	WEEK	1129.31229	2	564.65614	2.23	0.1335
	WA	846.49473	2	423.24737	1.67	0.2131
3	ERROR	5062.69288	20	253.13464		
	DW	567.95643	6	94.65940	0.45	0.8405
	DWA	1385.96396	6	230.99399	1.10	0.3709
4	ERROR	12556.54962	60	209.27583		
	TIME	744.77000	2	372.38500	0.71	0.5021
	TA	433.83125	2	216.91562	0.42	0.6656
5	ERROR	10441.43593	20	522.07180		
	DT	444.32937	6	74.05489	0.62	0.7172
	DTA	1421.31727	6	236.88621	1.97	0.0845
6	ERROR	7222.53738	60	120.37562		
	WT	124.93247	4	31.23312	0.37	0.8287
	WTA	140.86689	4	35.21672	0.42	0.7954
7	ERROR	3378.10982	40	84.45275		
	DWT	887.65951	12	73.97163	1.06	0.4028
	DWTA	1488.69598	12	124.05800	1.77	0.0603
8	ERROR	8400.41531	120	70.00346		

Appendix 2:2 Analysis of variance of Auditory Vigilance Task data: percent correct detections for final 40min

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
1	MEAN	435.66772	1	435.66772	0.26	0.6203
	AGE	0.60077	1	0.60077	0.00	0.9852
	ERROR	16674.66377	10	1667.46638		
2	DRUG	4345.78383	3	1448.59461	3.30	0.0337
	DA	1077.70741	3	359.23580	0.82	0.4940
	ERROR	13170.45457	30	439.01515		
3	WEEK	1621.17581	2	810.58790	2.55	0.1033
	WA	1757.19916	2	878.59958	2.76	0.0873
	ERROR	6361.88486	20	318.09424		
4	DW	903.81353	6	150.63559	0.47	0.8221
	DWA	1741.54025	6	290.25671	0.90	0.4993
	ERROR	19297.39855	60	321.62331		
5	TIME	34.18683	2	17.09341	0.03	0.9720
	TA	1069.88292	2	534.94146	0.89	0.4259
	ERROR	12006.68943	20	600.33447		
6	DT	3108.59389	6	518.09898	0.82	0.5584
	DTA	4303.59273	6	717.26545	1.14	0.3523
	ERROR	37883.14978	60	631.38583		
7	WT	447.91092	4	111.97773	1.01	0.4143
	WTA	413.98345	4	103.27086	0.93	0.4560
	ERROR	4439.30826	40	110.98271		
8	DWT	1277.07194	12	106.42266	0.90	0.5540
	DWTA	3033.12668	12	253.59972	2.13	0.0195
	ERROR	14267.90123	120	118.89918		

Appendix 2:3 Analysis of variance of Auditory Vigilance Task data: false positive responses over 1h

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	3948.23148	1	3948.23148	54.45	0.0000
	AGE	370.37037	1	370.37037	5.11	0.0474
1	ERROR	725.12037	10	72.51204		
	DRUG	105.80556	3	35.26852	1.07	0.3755
	DA	194.85185	3	64.95062	1.98	0.1387
2	ERROR	986.50926	30	32.88364		
	WEEK	15.00463	2	7.50231	0.71	0.5033
	WA	11.83796	2	5.91898	0.56	0.5795
3	ERROR	211.10185	20	10.55509		
	DW	44.06944	6	7.34491	1.22	0.3083
	DWA	55.49537	6	9.24923	1.54	0.1816
4	ERROR	360.93519	60	6.01559		
	TIME	18.35185	2	9.17593	1.08	0.3594
	TA	37.79630	2	18.89815	2.22	0.1347
5	ERROR	170.29630	20	8.51481		
	DT	24.94444	6	4.15741	1.16	0.3389
	DTA	48.98148	6	8.16358	2.28	0.0476
6	ERROR	214.74074	60	3.57901		
	WT	32.37037	4	8.09259	1.47	0.2279
	WTA	11.03704	4	2.75926	0.50	0.7338
7	ERROR	219.48148	40	5.48704		
	DWT	41.38889	12	3.44907	0.63	0.7680
	DWTA	136.46296	12	11.37191	2.24	0.0137
8	ERROR	608.81481	120	5.07346		

Appendix 2:4 Analysis of variance of Digit Symbol Substitution test data: items correctly coded

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	26164.45370	1	26164.45370	10.84	0.0081
	AGE	2966.25926	1	2966.25926	1.23	0.2937
1	ERROR	24146.67593	10	2414.66759		
	DRUG	11244.99074	3	3748.33025	1.38	0.2680
	DA	2662.37037	3	887.45679	0.33	0.8061
2	ERROR	81508.58333	30	2716.95278		
	WEEK	1267.31019	2	633.65509	1.53	0.2416
	WA	2096.44907	2	1048.22454	2.53	0.1052
3	ERROR	8302.35185	20	415.11759		
	DW	6067.18981	6	1011.19833	1.69	0.1793
	DWA	489.31019	6	81.55170	0.14	0.9910
4	ERROR	35925.38889	60	598.75648		
	TIME	23218.69907	2	11609.34954	5.69	0.0111
	TA	577.11574	2	288.55787	0.11	0.8899
5	ERROR	40801.78704	20	2040.08981		
	DT	12707.46759	6	2117.91127	0.75	0.6108
	DTA	7776.08796	6	1296.01466	0.46	0.8352
6	ERROR	169135.50000	60	2818.92500		
	WT	1409.66204	4	352.41551	0.74	0.5718
	WTA	1207.13426	4	301.78356	0.63	0.6427
7	ERROR	19106.09259	40	477.65231		
	DWT	5969.56019	12	497.46335	0.55	0.8810
	DWTA	12602.93981	12	1050.91165	1.16	0.3211
8	ERROR	108514.61111	120	912.62176		

Appendix 2:5 Analysis of variance of Card Sorting data: movement time into two categories

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
1	MEAN	4.77751	1	4.77751	0.30	0.5936
	AGE	2.60867	1	2.60867	0.17	0.6924
	ERROR	157.24946	10	15.72495		
2	DRUG	53.20646	3	17.73549	1.37	0.2706
	DA	76.51251	3	25.50417	1.97	0.1395
	ERROR	388.15583	30	12.93853		
3	WEEK	72.15979	2	36.07990	11.64	0.0004
	WA	0.80318	2	0.40159	0.13	0.8792
	ERROR	61.96812	20	3.09841		
4	DW	6.51804	6	1.08634	0.26	0.9514
	DWA	17.82489	6	2.97082	0.72	0.6329
	ERROR	246.64279	60	4.11071		
5	TIME	10.13915	2	5.06957	1.05	0.3698
	TA	8.84089	2	4.42045	0.91	0.4168
	ERROR	96.65389	20	4.83269		
6	DT	17.73552	6	2.95592	0.68	0.6613
	DTA	34.53640	6	5.75607	1.33	0.2581
	ERROR	259.85335	60	4.33089		
7	WT	6.49906	4	1.62477	0.59	0.6701
	WTA	5.49365	4	1.37341	0.50	0.7353
	ERROR	109.70380	40	2.74259		
8	DWT	43.48620	12	3.62385	2.03	0.0269
	DWTA	18.52937	12	1.54411	0.87	0.5835
	ERROR	214.06119	120	1.78384		

Appendix 2:6 Analysis of variance of Card Sorting data: movement time into four categories

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	29.68880	1	29.68880	1.97	0.1903
	AGE	18.68755	1	18.68755	1.24	0.2910
1	ERROR	150.39760	10	15.03876		
	DRUG	52.98284	3	17.66095	1.89	0.1521
	DA	36.58724	3	12.19575	1.31	0.2907
2	ERROR	280.16956	30	9.33899		
	WEEK	24.92024	2	12.46012	5.82	0.0102
	WA	1.99378	2	0.99689	0.47	0.6343
3	ERROR	42.80013	20	2.14001		
	DW	11.19915	6	1.86486	0.63	0.7053
	DWA	7.47969	6	1.24661	0.42	0.8619
4	ERROR	177.50254	60	2.95838		
	TIME	16.36254	2	8.18127	1.63	0.2210
	TA	3.79073	2	1.89536	0.38	0.6904
5	ERROR	100.42841	20	5.02142		
	DT	22.30812	6	3.71802	0.56	0.7597
	DTA	29.56983	6	4.92830	0.74	0.6170
6	ERROR	397.81596	60	6.63027		
	WT	4.70087	4	1.17522	0.79	0.5373
	WTA	1.72205	4	0.43051	0.29	0.8826
7	ERROR	59.31417	40	1.48360		
	DWT	7.74598	12	0.64550	0.57	0.8642
	DWTA	17.24851	12	1.43738	1.26	0.2498
8	ERROR	136.63128	120	1.13859		

Appendix 2:7 Analysis of variance of Card Sorting data: movement time into eight categories

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
1	MEAN	10.75098	1	10.75098	1.10	0.3181
	AGE	4.49983	1	4.49983	0.46	0.5120
	ERROR	97.36476	10	9.73648		
2	DRUG	40.67688	3	13.55896	1.67	0.1947
	DA	78.08262	3	26.02754	3.20	0.0372
	ERROR	243.71752	30	8.12392		
3	WEEK	19.32212	2	9.66106	6.62	0.0062
	WA	0.19880	2	0.09940	0.07	0.9344
	ERROR	29.17791	20	1.45890		
4	DW	10.31837	6	1.71973	0.83	0.5501
	DWA	6.02521	6	1.00420	0.49	0.8165
	ERROR	124.05357	60	2.06756		
5	TIME	8.19085	2	4.09542	0.88	0.4293
	TA	2.15172	2	1.07586	0.23	0.7952
	ERROR	92.81464	20	4.64073		
6	DT	101.52247	6	16.92041	2.78	0.0188
	DTA	10.62750	6	1.77125	0.29	0.9309
	ERROR	365.29900	60	6.08832		
7	WT	1.42829	4	0.35707	0.27	0.8935
	WTA	4.94602	4	1.23651	0.95	0.4475
	ERROR	52.27926	40	1.30698		
8	DWT	12.72819	12	1.06068	0.95	0.5001
	DWTA	7.02494	12	0.58541	0.52	0.8954
	ERROR	133.95526	120	1.11629		

Appendix 2:8 Analysis of variance of Card Sorting data: two category sorting times

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
1	MEAN	13.98960	1	13.98960	1.84	0.2050
	AGE	2.35263	1	2.35263	0.31	0.5804
	ERROR	76.09833	10	7.60983		
2	DRUG	112.40504	3	37.46835	1.80	0.1677
	DA	73.91892	3	24.63964	1.19	0.3315
	ERROR	623.00539	30	20.76685		
3	WEEK	10.84114	2	5.42057	1.56	0.2341
	WA	9.28749	2	4.64375	1.34	0.2847
	ERROR	69.37648	20	3.46882		
4	DW	11.39987	6	1.89997	0.50	0.8035
	DWA	22.53646	6	3.75608	0.99	0.4372
	ERROR	226.54938	60	3.77582		
5	TIME	0.86290	2	0.43145	0.09	0.9189
	TA	5.22850	2	2.61425	0.47	0.6328
	ERROR	113.17797	20	5.65889		
6	DT	123.25274	6	20.54212	2.51	0.0310
	DTA	99.90829	6	16.65138	2.04	0.0747
	ERROR	490.85137	60	8.18086		
7	WT	9.79205	4	2.44801	1.08	0.3806
	WTA	7.81215	4	0.95304	0.42	0.7937
	ERROR	90.90802	40	2.27270		
8	DWT	46.02770	12	3.83564	1.47	0.1438
	DWTA	37.43640	12	3.11970	1.20	0.2925
	ERROR	312.56925	120	2.60474		

Appendix 2:9 Analysis of variance of Card Sorting data: four category sorting times

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	13.58231	1	13.58231	0.45	0.5170
	AGE	30.65603	1	30.65603	1.02	0.3368
1	ERROR	301.10554	10	30.11055		
	DRUG	109.02906	3	36.34302	2.26	0.1022
	DA	125.37896	3	41.79299	2.59	0.0709
2	ERROR	483.23873	30	16.10796		
	WEEK	0.19237	2	0.09618	0.04	0.9584
	WA	9.78274	2	4.89137	2.17	0.1406
3	ERROR	45.13157	20	2.25658		
	DW	19.38298	6	3.23050	0.76	0.6028
	DWA	5.64968	6	0.94161	0.22	0.9682
4	ERROR	254.47259	60	4.24121		
	TIME	20.12002	2	10.06001	0.60	0.5567
	TA	5.92108	2	2.96054	0.18	0.8386
5	ERROR	333.52119	20	16.67606		
	DT	87.41618	6	14.56936	1.15	0.3436
	DTA	35.74145	6	5.95741	0.47	0.8269
6	ERROR	758.26545	60	12.63776		
	WT	3.57660	4	0.89415	0.44	0.7813
	WTA	8.29008	4	2.07252	1.01	0.4127
7	ERROR	81.91391	40	2.04785		
	DWT	38.74003	12	3.22834	1.58	0.1058
	DWTA	56.73604	12	4.72800	2.32	0.0107
8	ERROR	244.92417	120	2.04103		

Appendix 2:10 Analysis of variance of Card Sorting data: eight category sorting times

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
1	MEAN	10.68797	1	10.68797	2.81	0.1217
	AGE	29.06296	1	29.06296	7.63	0.0200
	ERROR	38.06601	10	3.80660		
2	DRUG	82.10697	3	27.36899	1.24	0.3114
	DA	24.90456	3	8.30152	0.38	0.7701
	ERROR	660.32483	30	22.01083		
3	WEEK	8.49662	2	4.24831	1.79	0.1926
	WA	36.10207	2	18.05103	7.61	0.0035
	ERROR	47.45900	20	2.37295		
4	DW	10.28211	6	1.71369	0.39	0.8848
	DWA	6.39380	6	1.06563	0.24	0.9613
	ERROR	266.01941	60	4.43366		
5	TIME	8.01378	2	4.00689	0.39	0.6817
	TA	17.99025	2	8.99512	0.88	0.4315
	ERROR	205.20138	20	10.26007		
6	DT	88.48274	6	14.74712	0.75	0.6222
	DTA	115.12003	6	19.18835	0.95	0.4687
	ERROR	1216.33132	60	20.27219		
7	WT	21.17259	4	5.29315	2.12	0.0966
	WTA	6.53406	4	1.63352	0.65	0.6281
	ERROR	100.03676	40	2.50092		
8	DWT	69.44598	12	5.78716	1.66	0.0846
	DWTA	54.35741	12	4.52978	1.30	0.2282
	ERROR	418.68832	120	3.48907		

	SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	TAIL PROBABILITY
	MEAN	71.78521	1	71.78521	0.98	0.3450
	AGE	0.72521	1	0.72521	0.01	0.9226
1	ERROR	730.85928	10	73.08593		
	DRUG	89.52155	3	29.84052	0.97	0.4183
	DA	85.64896	3	28.54965	0.93	0.4378
2	ERROR	919.88533	30	30.66284		
	WEEK	82.87680	2	41.43840	9.50	0.0013
	WA	2.57681	2	1.28840	0.30	0.7474
3	ERROR	87.23916	20	4.36196		
	DW	24.52338	6	4.08723	0.60	0.7262
	DWA	56.74041	6	9.45674	1.40	0.2308
4	ERROR	406.18782	60	6.76980		
	TIME	33.38430	2	16.69215	1.58	0.2306
	TA	2.30514	2	1.15257	0.11	0.8972
5	ERROR	211.26665	20	10.56333		
	DT	105.16810	6	17.52802	2.28	0.0475
	DTA	57.81430	6	9.63572	1.25	0.2920
6	ERROR	460.80588	60	7.68010		
	WI	6.77014	4	1.69253	0.55	0.6974
	WTA	3.21847	4	0.80462	0.26	0.8998
7	ERROR	122.26025	40	3.05651		
	DWI	21.82801	12	1.81900	0.64	0.8026
	DWTA	72.50405	12	6.04207	2.13	0.0195
8	ERROR	340.01372	120	2.83345		

Appendix 3 (over). Visual Analogue Scales used in Experiment 1

Appendix 3:1

Subject's code no. | | | |

Study day | | | |

ame.....Date.....

lorning Form

QUALITY OF SLEEP

Please make a mark on the line to indicate how well or how badly you feel you slept last night. A mark in the centre would mean an average, normal night, a mark to the left a poor night, a mark to the right a better night.

Worst possible ——— Best ever

MORNING VIGILANCE

Please make a mark on the line to show how bright, fresh and alert you feel this morning.

A normal, average sort of feeling should mean a mark in the centre. If you feel unusually bright and full of zest your mark should be to the left of centre, if unusually dull, drowsy or lethargic your mark should be to the right.

Marvellously alert and energetic ——— Awfully sleepy and lack-lustre

Appendix 3:2

Subject's code no. | | | |

Study day | | | |

ame ..... Date .....

ening Form

ANXIETY

Please indicate, by a mark on the line, how calm or anxious you have felt mentally today. An average day should mean a mark in the centre.

Terrible agitation ——— Utterly calm and peaceful

CONCENTRATION

Please indicate, by a mark on the line, how well you have felt able to concentrate mentally today. An average day should mean a mark in the centre.

Extremely difficult to concentrate ——— Wonderfully alert and penetrating mind

Appendix 4:1 (over). Census Returns used in Surveys 1 and 2

Appendix 4:1

HYPNOTIC DRUG CENSUS RETURN FOR MIDNIGHT, TUESDAY, 31st MARCH, 1981

HOME: _____

This information is being collected by the Social Work Department for all residents in its OPHs at the above date, to coincide with the SWSG collection of data on resident handicap and infirmity. Please list residents in the same order as the SWSG return.

			Complete where hypnotic drug used			
Line No.	Date of Birth	HYPNOTIC/SEDATIVE DRUG Give name if such a drug is used, or write 'NONE' if not used	Dose Given	Place 'X' if also given on previous night	Concomitant Medication with tranquillizers/ anti-depressants/ anti-convulsant drugs	
					Name of Drug	Daily Dosage
01						
02						
03						
04						
05						
06						
07						
08						
09						
10						
11						
12						
13						
14						
15						
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Appendix 4:2. Drug glossary used in hypnotic drug surveys (1980-81)

Hypnotic Drug Census

Trade names are given in the left hand column, pharmaceutical names appear in brackets. This list is not exhaustive. If you are in doubt, consult an alternative source (e.g. MIMS).

Hypnotic

Dalmane (flurazepam)
Doriden (glutethimide)
Euhypnos (temazepam)
Normison (")
Halcion (triazolam)
Heminevrin (chlormethiazole)
Mandrax (methaqualone)
Medomin (heptabarbitone)
Mogadon)
Somnite)
Nitrados) (nitrazepam)
Remnos)
Somnased)
Nembutal (pentobarbitone)
Noctec (chloral hydrate)
Seconal (quinalbarbitone)
Sodium Amytal (amylobarbitone)
Soneryl (butobarbitone)
Tuinal (quinalbarbitone)
Welldorm (dichloralphenazone)

Sedatives/Tranquillizers

Amytal (amylobarbitone)
Atensine (diazepam)
Ativan (lorazepam)
Cyclomet (cyclobarbitone)
Droleptan (droperidol)
Equanil (meprobamate)
Evacalm (diazepam)
Fentazin (perphenazine)
Frisium (clobazam)
Haldol (haloperidol)
Heminevrin (chlormethiazole)
Inderal (propranalol)
Largactil (chlorpromazine)
Librium (chlordiazepoxide)
Limbitrol (amitriptyline)
Luminal (phenobarbitone)
Melleril (thioridazine)
Miltown (meprobamate)
Prothiaden (dothiepin)

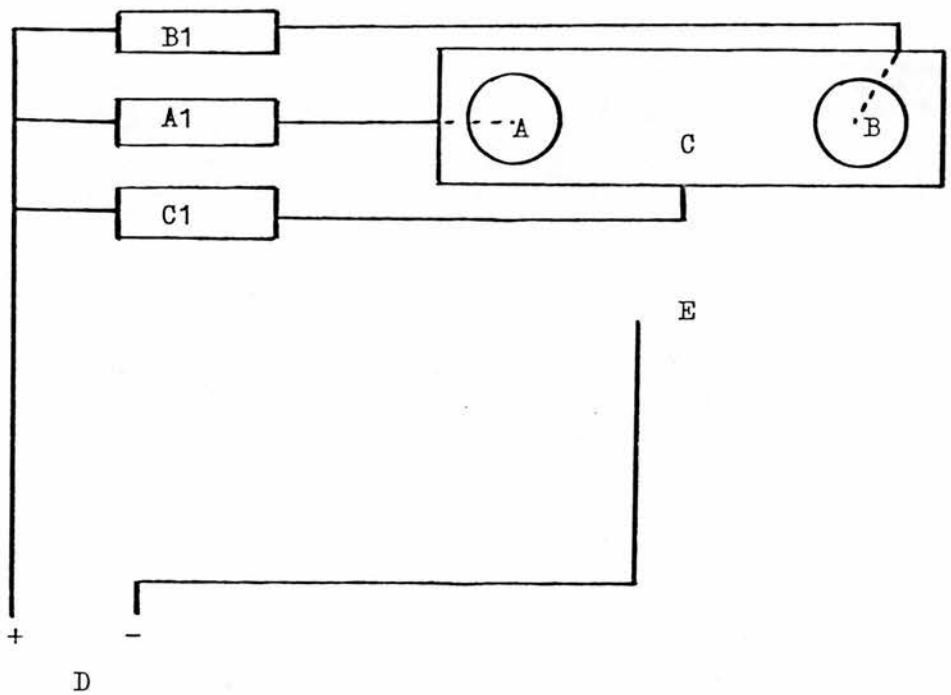
Sedatives/Tranquillizers

Seconal (quinalbarbitone)
Serenace (haloperidol)
Serenid (oxazepam)
Sinequan (doxepin)
Sodium Amytal (amylobarbitone)
Sparine (promazine)
Stelazine (trifluoperazine)
Stemetil (prochlorperazine)
Trancopal (chlormezanone)
Valium (diazepam)

Antidepressants

Allegron (nortriptyline)
Anafranil (clomipramine)
Aventyl (nortriptyline)
Berkomine (imipramine)
Bolvidon (mianserin)
Camcolit (lithium carbonate)
Concordin (protriptyline)
Domicol (amitriptyline)
Lentizol (")
Liskonum (lithium carbonate)
Marplan (isocarboxazid)
Norval (mianserin)
Optimax (l-tryptophan)
Parnate (tranylcypromine)
Parstelin (")
Pertofran (desipramine)
Phasal (lithium carbonate)
Prothiaden (dothiepin)
Saroten (amitriptyline)
Sinequan (doxepin)
Tofranil (imipramine)
Tryptizol (amitriptyline)

Appendix 5:1



Key

A) Left Target
B) Right Target
C) Fascia
A1) Digital event recorder for target A
B1) " " " " " B
C1) " " " " fascia
D) 6v power source
E) Hand-Held Stylus

Contact between the stylus (E) and either of the targets (A,B) is recorded as a 'hit' on A1 and B1 respectively. Contact between the stylus and the fascia is recorded as an 'error' on C1.

Dimensions

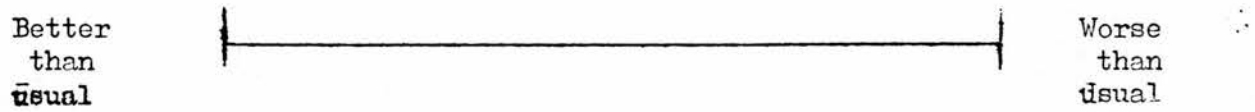
Tapping Board (i.e. Fascia): 20.5cm x 45.5cm
Targets: from 1.5cm to 6cm in diameter
Distance between targets: 25cm centre to centre

Appendix 5:2 (over)

Visual Analogue rating scales used in Experiment 2

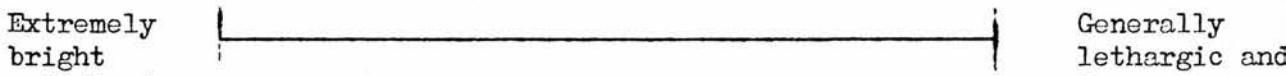
A mark in the centre of the line will mean 'no change'. If you have trouble arriving at a conclusion, consult other Care Workers, and come to a group decision.

1. Considering the time taken to get to sleep, the number of awakenings during the night, and the total duration of sleep, do you think the Resident slept:



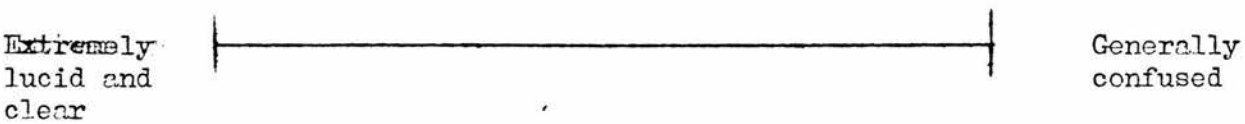
2. During the early part of the morning was the Resident:

3. Throughout the day has the resident been:



4. When observed walking about the Home has the Resident been:

5. Throughout the day do you think that the Resident has been:



NAME OF RESIDENT.....DATE.....

COMMENTS (Continence, untypical events)

Appendix 6:1 Visual Analogue rating scales used in Experiment 3

PLACE A MARK ON THE LINE AT A POINT WHICH CORRESPONDS WITH YOUR ANSWER

A MARK IN THE CENTRE OF THE LINE MEANS "NO CHANGE"

LAST NIGHT, DID YOU SLEEP:-

MUCH BETTER THAN USUAL? |———————————————————————————| MUCH WORSE THAN USUAL?

Name .....

Date .....

Place a mark on the line at a point which corresponds with your answer. A mark in the centre of the line means "no change". If you have trouble arriving at a conclusion, consult other Care Workers, and come to a group decision.

During the early part of the morning was the resident:-

Very alert |———————————————————————————| Very drowsy

Name .....

Date .....

Appendix 6:2 (over) Typical page of prose used for the letter cancellation task.

"They were very cunning, though. They must have thought that there was some chance of their being followed, for they would never go out alone, and never after nightfall. During two weeks I drove behind them every day, and never once saw them separate. Drebber himself was drunk half the time, but Stangerson was not to be caught napping. I watched them late and early, but never saw the ghost of a chance; but I was not discouraged, for something told me that the hour had almost come. My only fear was that this thing in my chest might burst a little too soon and leave my work undone.

"At last, one evening I was driving up and down Torquay Terrace, as the street was called in which they boarded, when I saw a cab drive up to their door. Presently some luggage was brought out and after a time Drebber and Stangerson followed it, and drove off. I whipped up my horse and kept within sight of them, feeling very ill at ease, for I feared that they were going to shift their quarters. At Euston Station they got out, and I left a boy to hold my horse and followed them on to the platform. I heard them ask for the Liverpool train, and the guard answer that one had just gone, and there would not be another for some hours. Stangerson seemed to be put out at that, but Drebber was rather pleased than otherwise. I got so close to them in the bustle that I could hear every word that passed between them. Drebber said that he had a little business of his own to do, and that if the other would wait for him he would soon rejoin him. His companion remonstrated with him, and reminded him that they had resolved to stick together. Drebber answered that the matter was a delicate one, and that he must go alone. I could not catch what Stangerson said to that, but the other burst out swearing, and reminded him that he was nothing more than his paid servant, and that he must not presume to dictate to him. On that the secretary gave it up as a bad job, and simply bargained with him that if he missed the last train he should rejoin him at Halliday's Private Hotel; to which Drebber answered that he would be back on the platform before eleven, and made his way out of the station.